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Synthesis of Cyclic α -Hydrazino Acid Derivatives via *N*-Acylhydrazonium Ions

Floris P.J.T. Rutjes, N. Miranda Teerhuis, Henk Hiemstra* and W. Nico Speckamp*

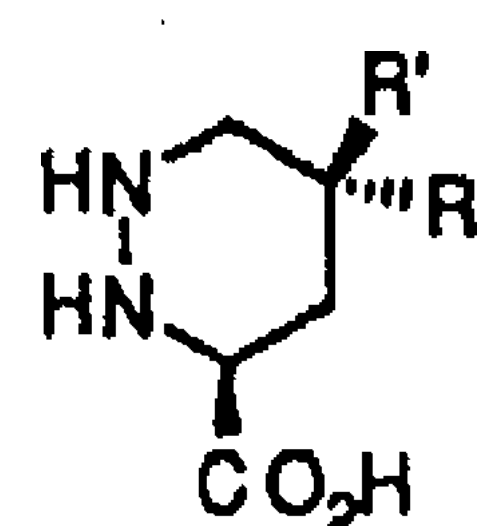
Laboratory of Organic Chemistry, University of Amsterdam
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

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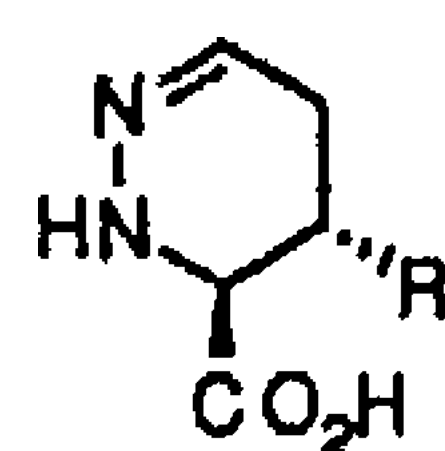
Abstract: The synthesis of various cyclic α -hydrazino esters is described. The key-step involves an intramolecular reaction of a highly reactive *N*-acylhydrazonium ion, leading to a cyclic cationic intermediate which either rearranges via an aziridinium ion, or leads to the unrearranged piperazic ester. A deprotection sequence that furnishes the free α -hydrazino acids is detailed.

INTRODUCTION

Since the first discovery three decades ago,¹ various tetra- and hexahydro-3-pyridazinecarboxylic acids, or piperazic acids (Piz) have been isolated. As constituents of several biologically active peptides such as the cyclic peptides monamycin,² L-156,602³ and luzopeptin A,⁴ the acyclic antrimycins,⁵ cirratiomycins,⁶ azinothricin antitumor antibiotics⁷ and the recently discovered antibiotic mathlystatin B,⁸ these compounds constitute a novel subclass of cyclic amino acids. Some of the piperazic acids present in these peptides are shown below.



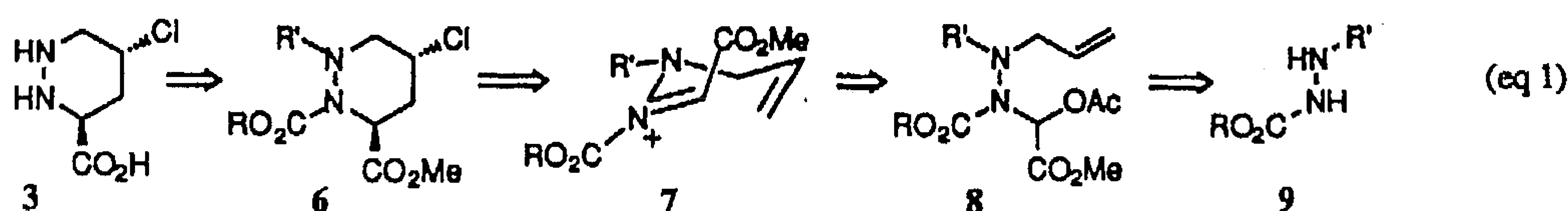
- 1 R = R' = H
2 R = H, R' = OH
3 R = Cl, R' = H



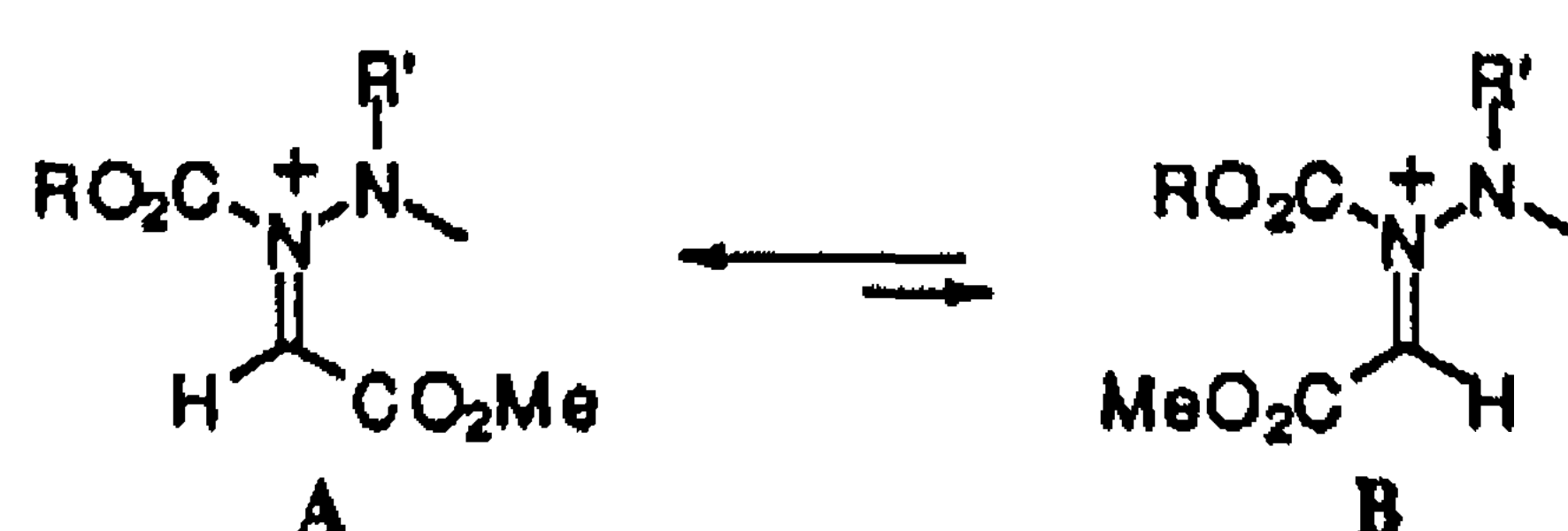
- 4 R = H
5 R = OH

The resemblance of these types of molecules with the corresponding α -amino acids suggests a promising potential as pharmacologically important compounds.^{9,10} Recently, several syntheses of cyclic hydrazino acids were reported among which piperazic acid 2 was synthesized via a hetero Diels-Alder reaction of a dienophile with an azo compound.¹¹ Furthermore, the acids 1, 4 and 5 were obtained via intramolecular condensations of enantiopure 2-hydrazino-5-oxo-pentanoic esters,¹²⁻¹⁵ the latter being prepared by enantioselective α -amination of enolates with an azodicarboxylate.¹⁶

Herein, we wish to report a novel approach to the synthesis of (racemic) cyclic α -hydrazino acids, which extends our previously reported work on *N*-acylhydrazonium ion cyclizations.¹⁷ For example, a sequence that is expected to lead to the chlorine substituted α -hydrazino acid 3 involves ring closure of 8 via the *N*-acylhydrazonium ion 7 to the protected α -hydrazino acid 6 (eq 1).



Comparison with well-investigated *N*-acyliminium ion cyclizations¹⁸ leads to the expectation that the cationic intermediate 7 will adopt a chair-like conformation, in which the *N*-acyliminium part has a (*Z*)-geometry. The preference for this geometry can be understood by considering the two possible conformations A and B of the hydrazonium ion. The (*E*)-isomer B is likely to be less stable as a result of *pseudo*-allylic 1,3-strain¹⁹ between the two carbonyl functions, which is absent in the (*Z*)-isomer A.

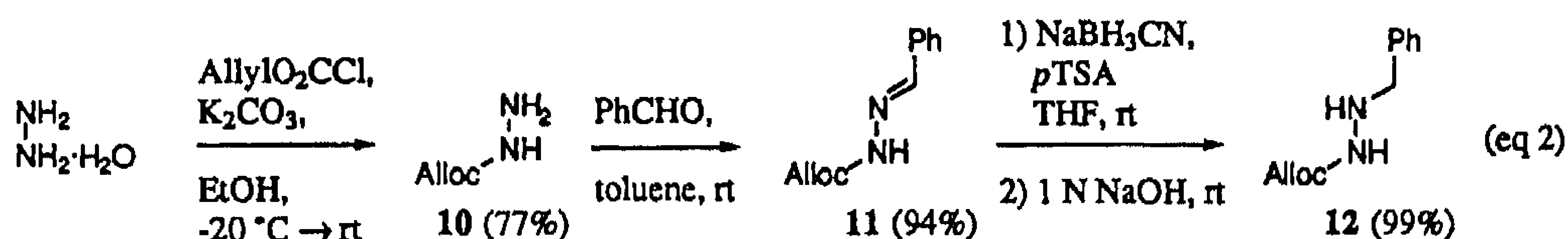


Attack of a nucleophile (*e.g.* chloride) on the intermediate π -complex of the olefin with the iminium ion will result in an overall *trans*-addition to the double bond, leading to the desired *trans*-relationship between the substituents in compound 6. The free hydrazine 3 might be obtained by deprotection of 6, in which R and R' are appropriate functional groups. The cyclization precursor 8 will be prepared from the suitably functionalized hydrazine 9 by alkylation with allyl bromide and methyl glyoxylate, respectively.

Moreover, introduction of various nucleophilic side chains will be shown to lead to the synthesis of numerous functionalized cyclic α -hydrazino acids of different ring sizes.

RESULTS AND DISCUSSION

The benzyl and allyloxycarbonyl (Alloc)²⁰ function were considered to be proper groups to functionalize both nitrogen atoms. In order to obtain the desired starting material 12, an excess of hydrazine hydrate was treated at -20 °C with allyl chloroformate to give allyl carbazate 10 (eq 2),²¹ which was readily purified by distillation. At lower temperatures, the reaction did not proceed whereas at higher temperatures the diacylated product was obtained. Because straightforward alkylation of 10 with benzyl chloride mainly led to dibenzylation of allyl carbazate (10), an alternative route was chosen for the synthesis of the monobenzylated carbazate 12.

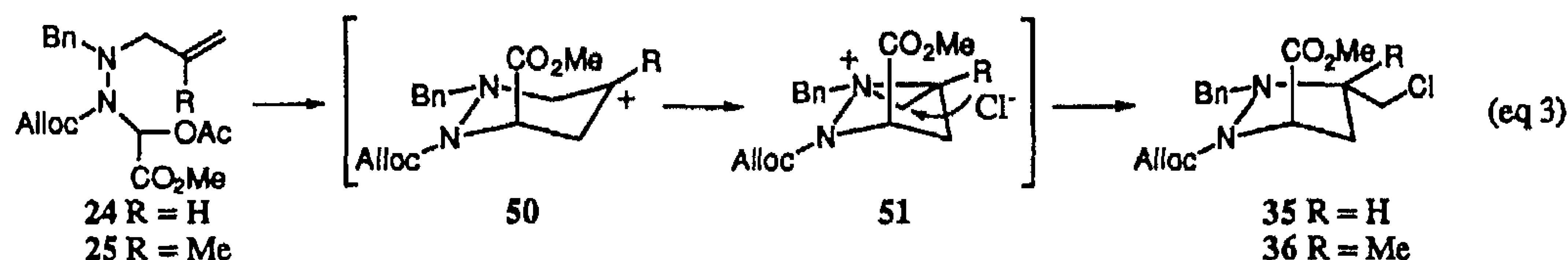


Thus, allyl carbazate (10) was condensed with benzaldehyde to give the hydrazone 11, which was reduced with NaBH₃CN to give 12 as its cyanoborane complex.²² Hydrolysis of the complex with NaOH afforded the monobenzylated carbazate 12. Distillation of 12 led to a dramatic decrease of the yield, so that crude 12 (virtually pure according to ¹H NMR data) was used for further reactions.

The functionalized hydrazine 12 was alkylated at the nucleophilic benzylic nitrogen atom with various halides as summarized in Table I (halide (1.1 equiv), K₂CO₃ (1.2 equiv), LiI (cat), butanone, acetone or ethanol, reflux). In general, reasonable to good yields were obtained for the activated halides. The less reactive butenyl bromide gave a lower yield (entry 8). Surprisingly, reaction of 12 with 4-iodo-1-(trimethylsilyl)-2-butyne^{23,24} under refluxing conditions led to desilylation of the propargylsilane moiety so that the allene 17 was

Introduction of the glyoxylate moiety was performed by stirring the alkylation product in the presence of anhydrous methyl glyoxylate.²⁹ The reaction rate of this condensation with glyoxylate proved to be strongly dependent on the steric bulk of the alkyl group. For example, the allyl precursor 13 (entry 1) reacted within 2 h to give the desired product, while for the benzyl precursor 19 (entry 9) a longer reaction time was required (up to 40 h). Because polymerization of unreacted methyl glyoxylate was a major side reaction, freshly distilled methyl glyoxylate had to be added after 18 h if the reaction was not completed. In some cases, large amounts (ca. 20 equiv) of methyl glyoxylate were used, so that purification by flash chromatography of the intermediate hydroxy compound was necessary. Acetylation (acetic anhydride (5 equiv), DMAP (cat), pyridine, rt) led to the cyclization precursors 24-34 in good yields as shown in Table I.

Cyclization of the allyl precursor **24** (entry 1) led to the unexpected formation of the five-membered rings **35** with the *trans*-isomer as the main product. These products cannot arise from a 'normal' 5-*exo*-type cyclization, because the chloromethyl substituent would then be at the 4-position. A possible explanation for the formation of **35** is detailed in eq 3. Presumably, cyclization initially gives rise to the formation of the secondary carbocation **50** (R = H), which is then trapped by the relatively nucleophilic N1 atom to give the aziridinium intermediate **51** (R = H). Attack of chloride gives ring opening of the aziridinium moiety, thus leading to the *trans*-azaproline derivative **35**. Similar types of ring contractions via aziridinium intermediates have been described in the literature.³⁰



It has been shown that in corresponding *N*-acyliminium cyclizations,¹⁸ the cationic intermediate is already formed at -78 °C and stabilized as a dioxycarbenium ion by the carbamate function (compare 53, eq 4). Quenching with saturated aqueous sodium bicarbonate at -78 °C then gives the corresponding hydroxy compound. In the case of these hydrazonium ions, such a sequence might block the rearrangement and directly give the precursor 54 for the piperazic acid 2. However, when the cyclization reaction of 24 was quenched with saturated aqueous sodium bicarbonate at -78 or at -30 °C, only starting material was recovered. Apparently, formation of the *N*-acylhydrazonium ion is more difficult than of its iminium analog. Reaction only took place at -20 °C (according to TLC), but quenching after stirring for 30 min at this temperature afforded a mixture of starting material and the rearranged products 35. This probably means that as soon as the intermediate cationic six-membered ring 50 (R = H) is formed, stabilization via the aziridinium intermediate 51 (R = H) takes place so that stabilization via the dioxycarbenium ion 53 does not occur.

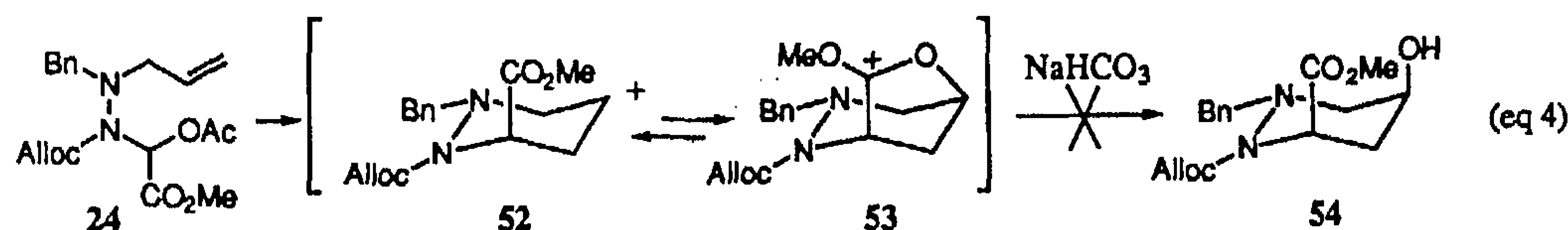
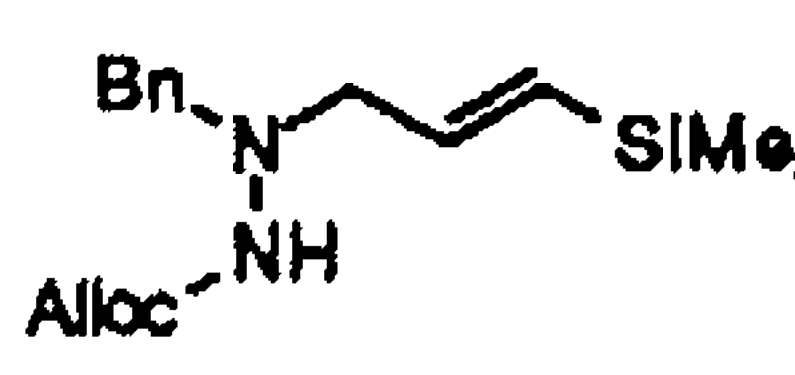
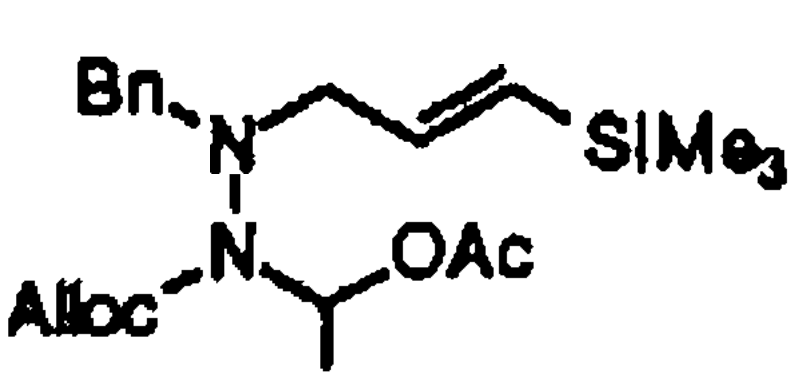
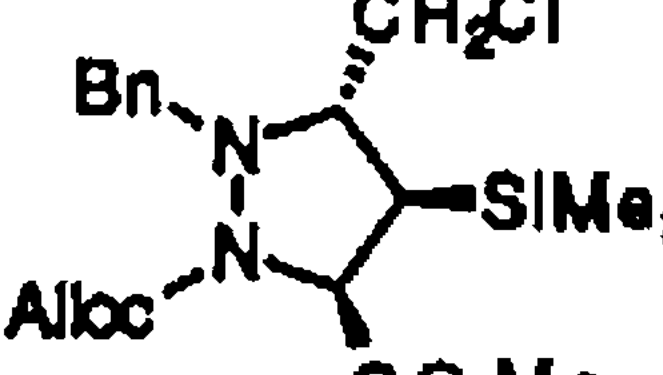
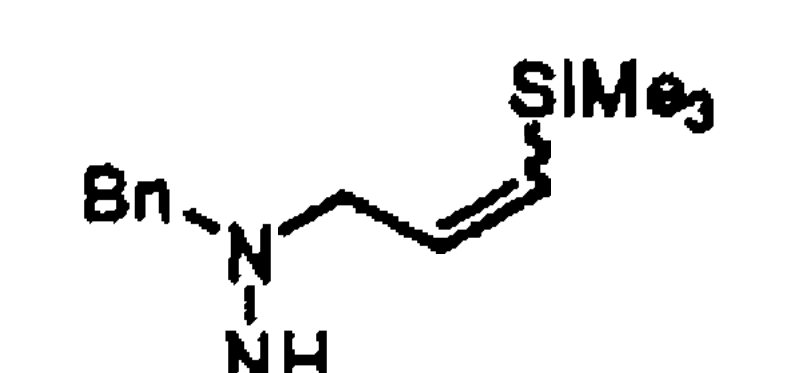
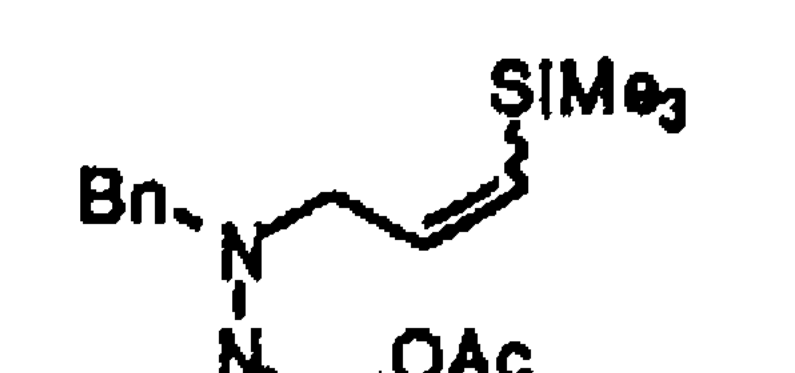
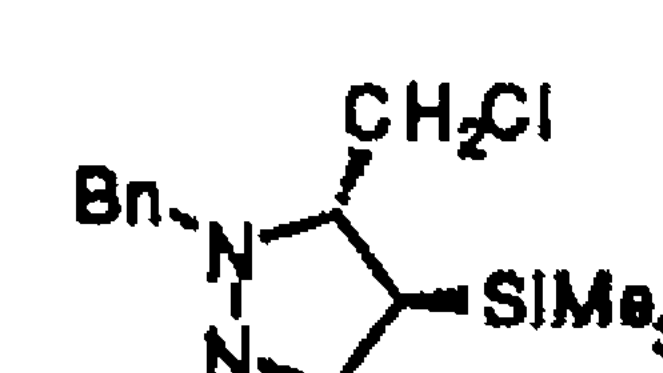
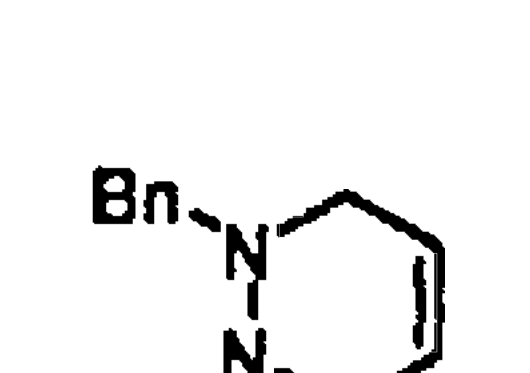


Table I. Synthesis of cyclic α -hydrazino acid derivatives.

entry	alkylation product (yield)	glyoxylate adduct (yield)	acid	cyclization products (yield)	
1	13 R = H (89%)	24 R = H (91%)	SnCl ₄	35 R = H (75%) <i>c/tr</i> 1:5	37 X = Cl (59%) <i>c/tr</i> 1:8.8
2	14 R = Me (78%)	25 R = Me (98%)	Et ₂ AlCl	36 R = Me (27%) <i>c/tr</i> 1:1.8	38 X = OCHO (68%) <i>trans</i>
3			HCOOH		
4	15 (66%)	26 (57%)	SnCl ₄	39 X = Cl (58%)	
5			HCOOH	40 X = OCHO (66%)	
6	16 (73%) (<i>E</i>)/(<i>Z</i>) 3.3:1	27 (82%) ^a	SnCl ₄	41 (56%) 5:1 mixture of isomers	
7	17 (23%)	28 (83%)	TiCl ₄	42 (45%) 1.2:1 mixture of isomers	
8	18 (39%)	29 (48%)	SnCl ₄	43 (65%) 1:1 mixture of isomers	
9	19 (83%) ^b	30 (99%)	SnCl ₄	44 (91%)	
10	20 (58%)	31 (79%)	Et ₂ AlCl	45 (83%)	46 (70%)
11			CF ₃ COOH		
12	21 (81%)	32 (82%)	BF ₃ ·OEt ₂	47 (30%)	

Table I (continued). Synthesis of cyclic α -hydrazino acid derivatives.

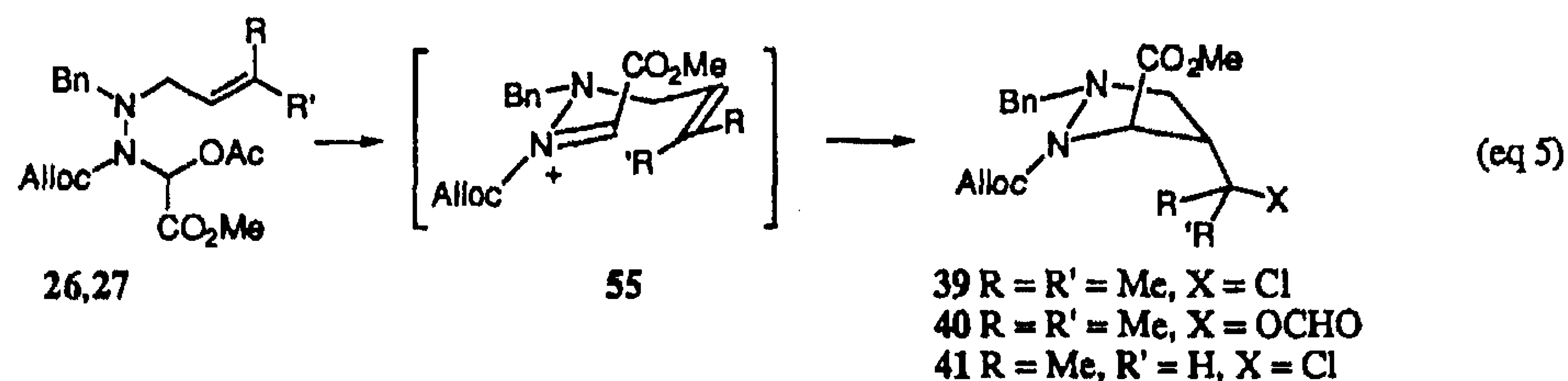
entry	alkylation product (yield)	glyoxylate adduct (yield)	acid	cyclization products (yield)
13	 22 (88%)	 33 (74%)	SnCl ₄	 48 (68%)
14	 23 (52%) (<i>E</i> / <i>Z</i>) 1:1.9	 34 (79%) (<i>E</i> / <i>Z</i>) 1:1.2	SnCl ₄	 48 (32%)  49 (50%)

a) The (*E*/*Z*)-ratio could not be determined from the ¹H NMR spectrum. b) Yield in one step from allylcarbazate (10).

The formation of the *trans*-five-membered ring was confirmed by reduction of the *trans*-cyclization product 35 with tri-*n*-butyltin hydride to give 56 (Chart 1), clearly showing the characteristic doublet of the methyl substituent in the ¹H NMR spectrum (0.98 ppm, d, *J* = 7.1 Hz). The structure was further proven by an X-ray crystallographic analysis of the deprotected product 66 (Fig 1). The formation of the *cis*-five-membered ring product 35 was concluded by comparison of the ¹³C NMR data of the *cis*- and *trans*-isomers of 35.

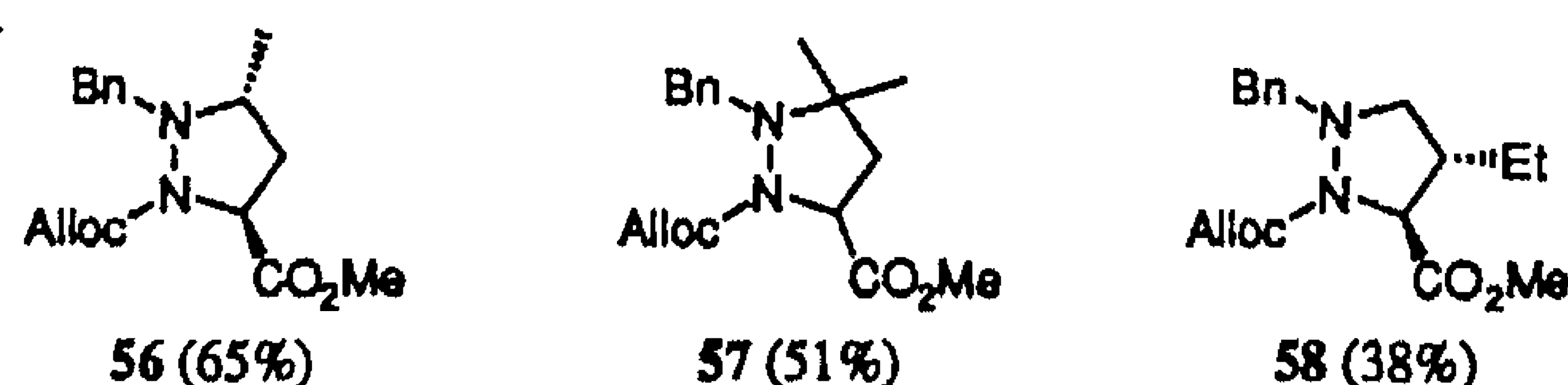
An analogous mechanism in the case of the methallyl substituent 25 (entry 2) accounts for the formation of the mixture of the five- and six-membered rings 36 and 37, respectively. The formation of the five-membered rings 36 was proven by reduction of the mixture with tri-*n*-butyltin hydride to give 57 (Chart 1). The relative configuration of *trans*-36 was secured by NOE difference ¹H NMR techniques. Irradiation of the methylene group adjacent to the chlorine atom showed an enhancement of H3, whereas irradiation of the methyl function did not. The more stable tertiary carbocation 50 (*R* = Me, eq 3) is less prone to be stabilized by the nitrogen atom and thus leads to a considerable amount of the six-membered rings 37. The stereochemistry of the *cis*- and *trans*-products was assigned by subjecting *trans*-37 to NOE difference ¹H NMR techniques; irradiation of the methyl function showed an enhancement of the signal of one of the H6 protons and of the broad signal of both H4 protons. The fact that the signal of only one of the H6 protons was enhanced leads to the conclusion that the methyl group is in the axial position. In view of the proposed conformation of the intermediate hydrazone species, the ester function is expected to be axially oriented. When formic acid was used for the cyclization (entry 3), only the *trans* six-membered ring 38 was found. The tertiary carbocation 50 (*R* = Me) probably gives a faster reaction with formate as a result of the large excess of the nucleophile so that ring contraction is less likely to occur.

Cyclization of the prenyl precursor 26 (entries 4 and 5) afforded the expected five-membered rings 39 and 40 with a *trans*-relationship between both substituents. Surprisingly, the crotyl precursor 27 (entry 6) also gave only a mixture of the *trans*-five-membered ring products 41.

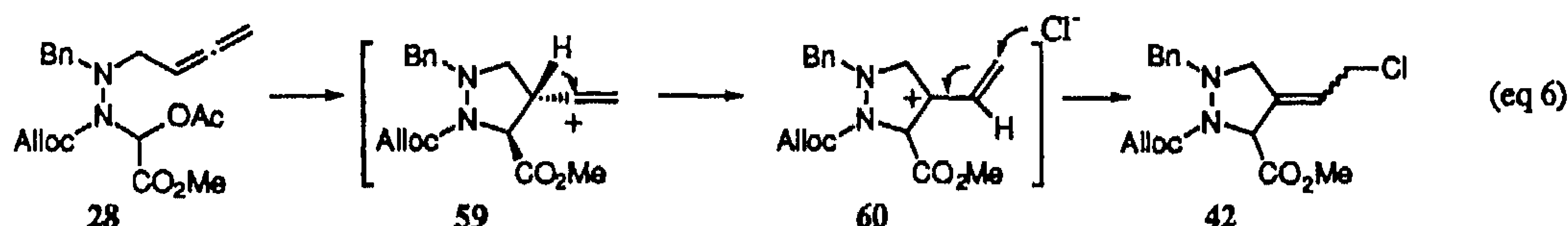


The *trans*-relationship between the substituents of the products 39, 40 and 41 is in accordance with the expected chair-like conformation 55 leading to the most favorable transition state (eq 5). The preference for the formation of a five-membered ring in the case of the crotyl precursor 27 is remarkable, because in similar cationic cyclizations six-membered rings are generally obtained. For example, comparable *N*-acyliminium ion precursors led to exclusive formation of six-membered rings.^{18b} Reduction of the cyclization product 41 with tri-*n*-butyltin hydride afforded 58, thus confirming the formation of the five-membered ring. The *trans*-orientation was deduced from NOE difference ¹H NMR techniques. Irradiation of the methyl substituent of 41 showed an enhancement of the signal of H3.

Chart I

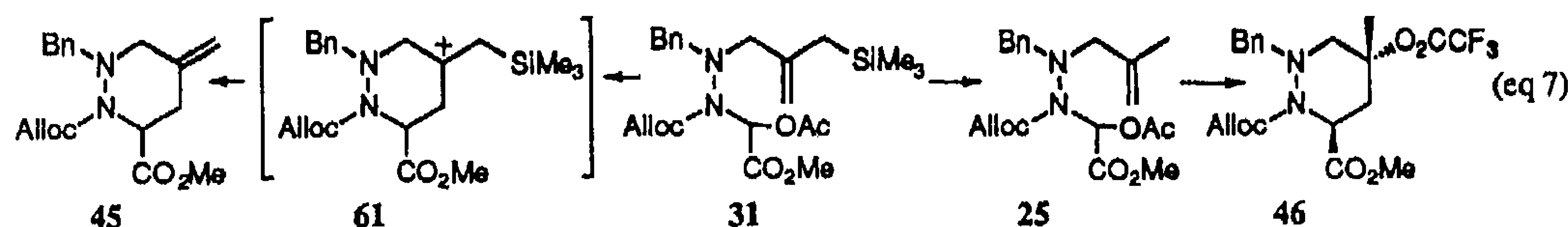


Additional evidence for the preference for the formation of five-membered rings was obtained upon cyclization of the allene precursor 28 (entry 7). Treatment of 28 with titanium tetrachloride afforded the five-membered rings 42 as a mixture of (*E*)/(*Z*)-isomers that could not be separated by flash chromatography. A mechanism that accounts for the formation of 42 is shown in eq 6. Initially, cyclization takes place to afford the vinylic cation 59. This intermediate rearranges via a 1,2-H shift to the more stable tertiary allylic cation 60, which is trapped by chloride to afford 42.



The seven-membered rings 43 were obtained upon cyclization of the butenyl precursor 29 (entry 8). Cyclisation of the dibenzyl precursor 30 took place smoothly to give 44 in excellent yield (entry 9) although cyclisation involving the benzyl function was not observed in any of the other reactions in table I. This is remarkable and might be partly explained by the difference in nucleophilicity with the other substituents, but also by the strong preference for the formation of five-membered rings. Presumably, other systems are likely to adopt a conformation in which the relatively large benzyl function is moved away from the glyoxylate moiety and thus will be less available for cyclization.

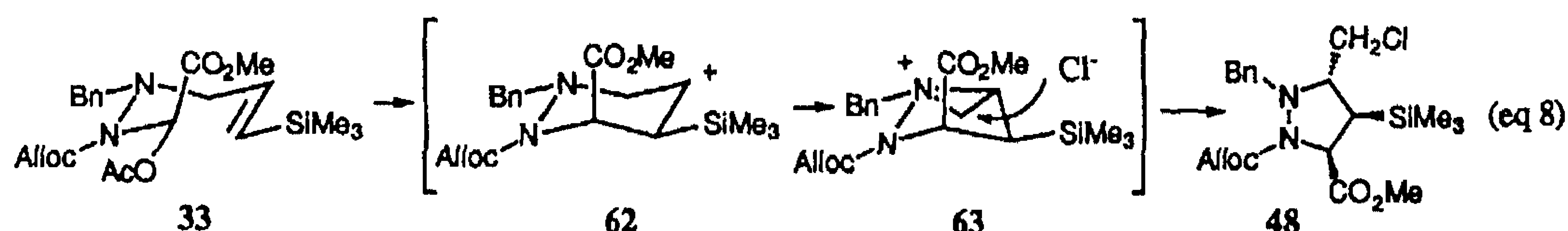
Another way to inhibit the ring contraction was observed upon cyclization of the allylsilane 31 (entry 10). Treatment with diethylaluminum chloride initially led to the silicon stabilized carbocation 61 (eq 7) which gave a fast elimination to the exocyclic double bond. An indication that formation of six-membered rings in such systems is a relatively slow process, is seen in entry 11. Treatment of the allylsilane precursor 31 with trifluoroacetic acid afforded 46 as a single product, which is explained by protodesilylation of 31 to the methallyl precursor 25 (not isolated), followed by cyclization to the expected six-membered ring 46 (treatment of 31 with formic acid gave the corresponding formate 38 in 58% yield).



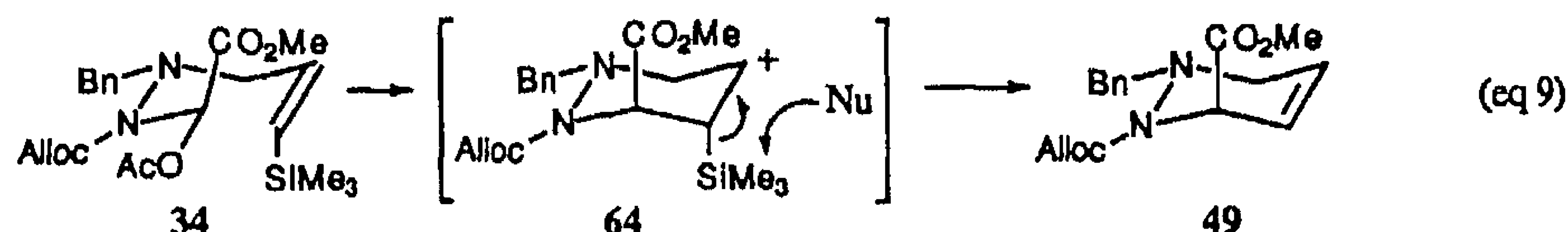
The fact that the cyclization product **45** appeared to be stable in formic acid indicates that the formation of **46** is not simply a result of addition of formic acid to the double bond after cyclization.

In an analogous way, the propargylsilane **32** (entry 12) was treated with boron trifluoride etherate to give the allene **47** in a rather poor yield.

A striking difference was observed between cyclization of the (*E*)- and (*Z*)-vinylsilanes **33** and **34** (entries 13 and 14). The chair-like transition state conformations of both starting materials are visualized in eqs 8 and 9, respectively. The (*E*)-vinylsilane **33** will react via a chair-like conformation to the cyclic cationic intermediate **62** in which the trimethylsilyl group occupies the equatorial position. Because the β -C-Si bond is not coplanar with the vacant *p*-orbital, stabilization of the positive charge by the silicon atom and subsequent elimination is not likely to take place, thus leading to a ring contraction via the aziridinium intermediate **63**. Attack of chloride affords the final product **48**. The stereochemistry of the product was confirmed by subjecting **48** to NOE difference ^1H NMR techniques, showing an enhancement of only H3 upon irradiation of the proton adjacent to the silicon atom.



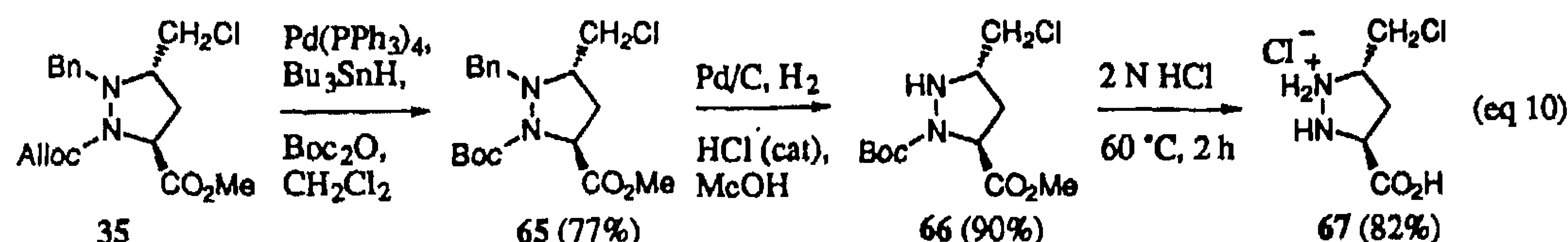
Cyclization of the (*Z*)-precursor **34** will occur via conformation **64** in which the trimethylsilyl group is axially oriented. In this orientation, maximal σ - π hyperconjugative stabilization of the developing positive charge is possible, followed by fast elimination to the unsaturated six-membered ring **49**, thereby excluding the formation of the aziridinium intermediate. Considering these mechanistic details, starting from the precursor **34**, that was obtained as a 1:1.2 mixture of (*E*)- and (*Z*)-isomers, the corrected yields for **48** and **49** (entry 14) are 70% and 90%, respectively. Comparing the yield of the five-membered ring product **48**, with the yield of **48** from the pure (*E*)-precursor **33** (entry 13), it is evident that the (*Z*)-isomer leads to exclusive formation of the six-membered ring **49**.



These observations are in full accord with results published by Overman and co-workers,³¹ who reported the (*Z*)-vinylsilane to be at least 7000 times more reactive than its (*E*)-analog in iminium ion cyclizations.

DEPROTECTION REACTIONS

The sequence of deprotection reactions developed for compound **35** is shown in eq 10. First, the Alloc group was converted into the acid-labile Boc group (eq 10) in a one-pot procedure via a so-called transprotection reaction [$\text{Pd}(\text{PPh}_3)_4$ (cat), Bu_3SnH (1,1 equiv), Boc_2O (2 equiv), CH_2Cl_2 , rt).²⁰



Hydrogenation of **65** {10% Pd/C, HCl (cat)} led to smooth removal of the benzyl group to give **66**, which was readily hydrolyzed to the HCl-salt **67** of the free α -hydrazino acid.

The structure of the five-membered ring **66**, including the *trans*-relationship between the substituents was secured by an X-ray crystallographic analysis of **66** as depicted in Fig I. Beside the *trans*-relationship, it clearly shows the difference between the almost planar carbamate nitrogen atom (N2) and the pyramidal amine nitrogen atom (N1).

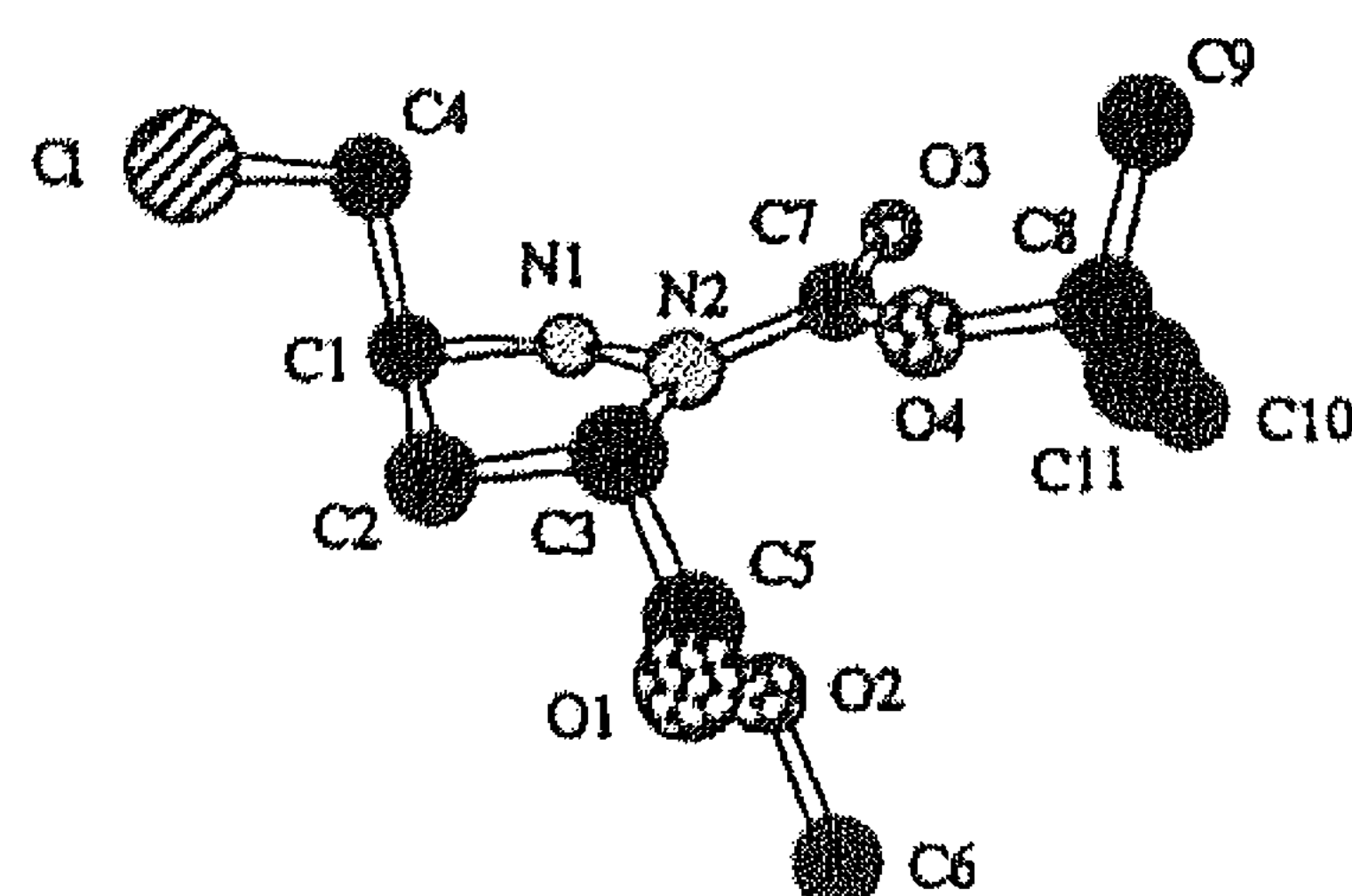


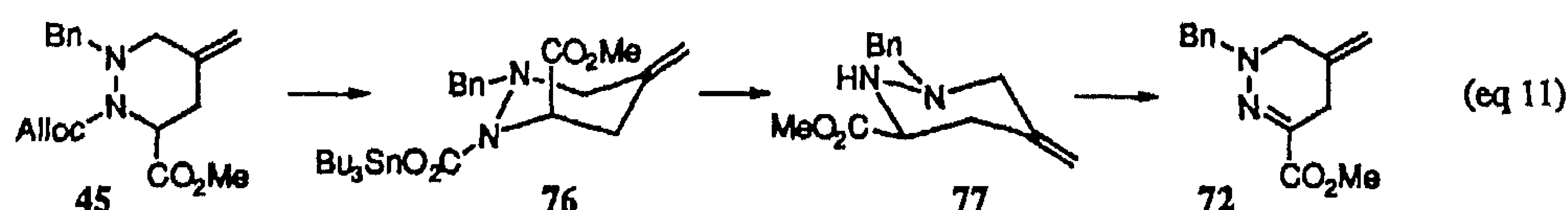
Figure I. Chem3D™ view of the crystal structure of **66** (hydrogens are not shown).

Some of the cyclization products were subjected to these deprotection reactions of which the results are summarized in Table II.

Table II. Deprotection reactions.

entry	cyclization product(s)	transprotection product(s) (yield)	reduction product(s) (yield)
1	 41	 68 (54%)	
2	 42	 69 (64%)	 74 (65%)
3	 44	 70 (56%)	 71 (22%)
4	 45	 72 (78%)	
5	 48	 73 (64%)	 75 (81%)

The desired transprotected products could not be obtained in all cases. Transprotection of the five-membered rings proceeded in reasonable yields (entries 1 and 5), whereas the six-membered rings **44** and **45** also gave deprotection of the Alloc group to give the corresponding oxidized products **71** and **72** (entries 3 and 4). Apparently, the reaction with di-*tert*-butyl dicarbonate is very sensitive to steric hindrance caused by the benzyl substituent and the methyl ester, which is more pronounced in the six-membered rings. The formation of the oxidized products might be explained by decarboxylation of the initially formed tin carbamate **76**,³² which will give a ring inversion to the thermodynamically more stable hydrazine **77** (eq 11).³³ Once the ring inversion has taken place, oxidation occurs to give **72**. Attempts to introduce smaller electrophiles like an acetyl function also failed.



The seven-membered ring **42** (entry 3), however, afforded the transprotected product **69** in a reasonable yield. Probably, the methyl ester causes less steric strain in a larger, more flexible ring.

Analogous to the hydrazino acid derivative **65**, debenzylation of **69** and **73** provided a good yield of the corresponding hydrazines **74** and **75** (entries 2 and 5).

CONCLUSIONS

It is evident that a large variety of cyclic α -hydrazino acid derivatives can be efficiently synthesized via this method. Several conclusions can be drawn from the outcome of the cyclization reactions. The cyclizations show a strong preference for the formation of five-membered rings, particularly illustrated by the crotyl and allene precursor, which both produced the corresponding five- instead of six-membered rings. Furthermore, if a six-membered ring is formed during the cyclization, stabilization of the cationic intermediate by the amine nitrogen atom may take place, leading to a five-membered ring via an aziridinium intermediate. This ring contraction can be inhibited by stabilization of the developing positive charge by a β -silicon substituent, followed by a fast elimination process. A remarkable difference in reactivity is observed between the benzyl group and the non-aromatic π -nucleophiles; cyclization of the benzyl group only takes place if no other nucleophile is present in the molecule. Deprotection is carried out by the transprotection method. This method fails in most six-membered ring cases, probably due to steric hindrance.

ACKNOWLEDGEMENT

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EXPERIMENTAL

All reactions were carried out under an inert atmosphere of dry nitrogen, unless otherwise described. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared (IR) spectra were obtained from CHCl_3 solutions, unless indicated otherwise, using a Perkin-Elmer 1310 spectrophotometer and wavenumbers (ν) are reported in cm^{-1} . Proton nuclear magnetic resonance (^1H NMR) spectra were determined in CDCl_3 (unless indicated otherwise) using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker AMX 300 (300 MHz) spectrometer. The latter three machines were also used for ^{13}C NMR (APT) spectra (50, 63 and 75 MHz respectively) in CDCl_3 (unless indicated otherwise). Chemical shifts (δ) are

given in ppm downfield from tetramethylsilane. Low and high resolution mass spectra were recorded by using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F₂₅₄) with the indicated solvent(mixture). Chromatographic purification refers to flash chromatography (fc)³⁴ using the same solvent as for TLC and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm). Melting and boiling points are uncorrected. CH₂Cl₂ was distilled from P₂O₅ and stored over MS 4Å under an atmosphere of dry nitrogen. TiCl₄ and SnCl₄ were distilled and stored under a dry nitrogen atmosphere as a solution in CH₂Cl₂. BF₃·OEt₂ was distilled and stored under a dry nitrogen atmosphere. Dry THF and Et₂O were distilled from sodium benzophenone ketyl prior to use.

Allyl carbazate (10). To a solution of hydrazine hydrate (128 mL, 2.64 mmol) in EtOH (1.3 L) was added dropwise in 1.5 h allyl chloroformate (70.0 mL, 0.66 mmol) while the temperature inside the flask was kept around -20 °C. The mixture was allowed to warm to rt, stirred at ambient temperature for 1 h and after addition of K₂CO₃ (91.2 g, 0.66 mol), it was stirred for an additional hour. After filtration and concentration *in vacuo*, the residue was distilled to afford 10 (59.2 g, 0.51 mol, 77%) as a colorless oil, bp 82 °C (0.3 mm), R_f 0.35 (ethyl acetate/hexane 1:1). IR ν 3460, 3350, 1710, 1625, 995, 935; ¹H NMR (200 MHz) δ 3.66 (br s, 2 H, NH₂), 4.56 (d, J = 5.6 Hz, 2 H, OCH₂), 5.15-5.31 (m, 2 H, =CH₂), 5.77-5.97 (m, 1 H, =CH), 6.61 (br s, 1 H, NH).

1-Benzyl-2-hydrazinecarboxylic acid allyl ester (12). To a solution of allyl carbazate (10), (10.0 g, 86.2 mmol) in toluene (170 mL) was added benzaldehyde (9.1 mL, 90.5 mmol) and the mixture was stirred at rt for 18 h. Filtration and recrystallization (ethyl acetate/hexane/methanol 5:10:1) afforded the hydrazone 11 (16.5 g, 80.9 mmol, 94%) as white crystals, mp 147-148 °C. IR ν 3400, 3340, 1730, 690; ¹H NMR (250 MHz) δ 4.64 (d, J = 5.4 Hz, 2 H, OCH₂), 5.24-5.41 (m, 2 H, =CH₂), 5.90-6.06 (m, 1 H, =CH), 7.24 (s, 1 H, ArH), 7.34 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.86 (s, 1 H, NH), 8.01 (s, 1 H, N=CH). A solution of pTSA (23.6 g, 124 mmol) in THF (125 mL) was added dropwise in 2.5 h to a solution of the hydrazone 11 (25.3 g, 124 mmol) and NaBH₃CN (9.18 g, 124 mmol) in THF (300 mL) and the mixture was stirred for one additional hour at rt. The resulting mixture was diluted with ethyl acetate (600 mL) and extracted subsequently with aq satd NaCl (600 mL), aq satd NaHCO₃ (600 mL) and aq satd NaCl (600 mL). The organic layer was dried (MgSO₄), filtered, concentrated *in vacuo*, taken up in 1 N NaOH (250 mL), stirred at ambient temperature for 1.5 h, neutralized with 2 M HCl and extracted with CH₂Cl₂ (3 \times 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford 12 (25.3 g, 123 mmol, 99%) as a colorless oil, R_f 0.45 (ethyl acetate/hexane 4:1). IR ν 3440, 3340, 1710, 990, 930, 690; ¹H NMR (200 MHz) δ 4.00 (s, 2 H, CH₂Ph), 4.25 (br s, 1 H, NH), 4.61 (d, J = 5.5 Hz, 2 H, OCH₂), 5.20-5.35 (m, 2 H, =CH₂), 5.82-6.01 (m, 1 H, =CH), 6.44 (br s, 1 H, NH), 7.26-7.36 (m, 5 H, ArH).

General procedure A for the alkylation reactions. To a solution of 12 in 2-butanone, EtOH or acetone were added the alkylating agent (1.1-2 equiv), K₂CO₃ (1.1-2 equiv) and a catalytic amount of LiI. After heating at reflux temperature for 18 h, the mixture was concentrated *in vacuo*, taken up in H₂O and extracted with CH₂Cl₂ (3 \times). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and purified by fc to afford the pure alkylated hydrazine.

1-Benzyl-1-(2-propenyl)-2-hydrazinecarboxylic acid allyl ester (13). Following the general procedure A, 12 (3.00 g, 14.6 mmol) was alkylated by using allyl bromide (3.52 g, 29.1 mmol) and K₂CO₃ (2.00 g, 14.6 mmol) in EtOH (100 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded 13 (3.20 g, 13.0 mmol, 89%) as a white solid, mp 34-36.5 °C, R_f 0.30. IR ν 3430, 3330, 1720, 690; ¹H NMR (200 MHz) δ 3.45 (br s, 2 H, NCH₂), 3.99 (br s, 2 H, CH₂Ph), 4.52 (d, J = 5.4 Hz, 2 H, OCH₂), 5.15-5.28 (m, 4 H, 2 \times =CH₂), 5.76-6.03 (m, 3 H, 2 \times =CH and NH), 7.30-7.35 (m, 5 H, ArH).

1-Benzyl-1-(2-methyl-2-propenyl)-2-hydrazinecarboxylic acid allyl ester (14). According to the general procedure A, **12** (10.0 g, 48.5 mmol) was alkylated by using 3-chloro-2-methyl-2-propene (5.28 mL, 53.4 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in EtOH (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **14** (9.81 g, 37.7 mmol, 78%) as a light yellow oil, R_f 0.30. IR ν 3440, 3340, 1720, 695; 1H NMR (200 MHz) δ 1.83 (s, 3 H, CH_3), 3.41 (br s, 2 H, NCH_2), 4.02 (br s, 2 H, CH_2Ph), 4.53 (d, $J = 5.2$ Hz, 2 H, OCH_2), 4.90 (d, $J = 6.6$ Hz, 2 H, $C=CH_2$), 5.16-5.28 (m, 2 H, $CH=CH_2$), 5.75-5.95 (m, 2 H, $=CH$ and NH), 7.26-7.38 (m, 5 H, ArH).

1-Benzyl-1-(3-methyl-2-butenyl)-2-hydrazinecarboxylic acid allyl ester (15). According to the general procedure A, **12** (7.04 g, 34.2 mmol) was alkylated by using 4-bromo-2-methyl-2-butene (5.60 g, 37.6 mmol) and K_2CO_3 (5.20 g, 37.6 mmol) in EtOH (300 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **15** (2.89 g, 10.5 mmol, 66% (after correction)) as a light yellow oil, R_f 0.40. IR ν 3440, 3340, 1725, 690; 1H NMR (200 MHz) δ 1.63 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 3.45 (br s, 2 H, NCH_2), 3.97 (br s, 2 H, CH_2Ph), 4.52 (d, $J = 5.3$ Hz, 2 H, OCH_2), 5.14-5.36 (m, 3 H, $=CH_2$ and NCH_2CH), 5.75-5.95 (m, 2 H, $=CH$ and NH), 7.23-7.34 (m, 5 H, ArH).

1-Benzyl-1-(2-butenyl)-2-hydrazinecarboxylic acid allyl ester (16). According to the general procedure A, **12** (10.0 g, 48.5 mmol) was alkylated by using 4-bromo-2-butene ((*E*)/(*Z*) 3.3:1, 5.28 mL, 53.4 mmol) and K_2CO_3 (7.38 g, 53.4 mmol) in EtOH (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **16** (9.18 g, 35.3 mmol, 73%) as a light yellow oil, (*E*)/(*Z*) 3.3:1, R_f 0.35. IR ν 3440, 3340, 1720, 690; 1H NMR (200 MHz) δ 1.64 (d, $J = 6.4$ Hz, 3 H, CH_3 (*Z*)), 1.70 (d, $J = 5.0$ Hz, 3 H, CH_3 (*E*)), 3.38 (br s, 2 H, NCH_2), 3.95 (br s, 2 H, CH_2Ph), 4.52 (d, $J = 5.3$ Hz, 2 H, OCH_2), 5.14-5.26 (m, 2 H, $=CH_2$), 5.45-5.92 (m, 4 H, $=CH$, NH and $CH=CH$), 7.26-7.32 (m, 5 H, ArH).

1-Benzyl-1-(ethenylidenemethyl)-2-hydrazinecarboxylic acid allyl ester (17). According to the general procedure A, **12** (2.32 g, 11.3 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne²⁴ (4.09 g, 12.4 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) in EtOH (100 mL). Work-up and fc (ethyl acetate/hexane 1:5) afforded **17** (670 mg, 2.60 mmol, 23%) as an orange oil, R_f 0.40. IR ν 3440, 3340, 1950, 1725, 690; 1H NMR (200 MHz) δ 3.64 (br s, 2 H, NCH_2), 4.00 (br s, 2 H, CH_2Ph), 4.54 (d, $J = 5.5$ Hz, 2 H, OCH_2), 4.76 (dt, $J = 6.5, 2.3$ Hz, 2 H, $C=CH_2$), 5.16-5.28 (m, 3 H, $CH=CH_2$ and $CH=C=CH_2$), 5.77-5.96 (m, 2 H, $=CH$ and NH), 7.27-7.36 (m, 5 H, ArH).

1-Benzyl-1-(3-butenyl)-2-hydrazinecarboxylic acid allyl ester (18). According to the general procedure A, **12** (2.91 g, 14.1 mmol) was alkylated by using 4-bromo-1-butene (2.10 g, 15.5 mmol) and K_2CO_3 (2.15 g, 15.5 mmol) in EtOH (150 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **18** (384 mg, 1.50 mmol, 39% (after correction)) as white crystals, mp 50-51 °C, R_f 0.45. IR ν 3440, 3340, 1740, 690; 1H NMR (200 MHz) δ 2.26-2.34 (m, 2 H, NCH_2CH_2), 2.70-2.95 (br s, 2 H, NCH_2), 3.80-4.15 (m, 2 H, CH_2Ph), 4.55 (d, $J = 5.4$ Hz, 2 H, OCH_2), 4.98-5.21 (m, 4 H, $2 \times =CH_2$), 5.55-5.95 (m, 3 H, $2 \times =CH$ and NH), 7.26-7.35 (m, 5 H, ArH).

1,1-Dibenzyl-2-hydrazinecarboxylic acid allyl ester (19). According to the general procedure A, **10** (15.0 g, 130 mmol) was alkylated by using benzyl chloride (29.7 mL, 260 mmol) and K_2CO_3 (36 g, 260 mmol) in EtOH (300 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **19** (31.9 g, 110 mmol, 83%) as a white solid, mp 52-54 °C, R_f 0.45. IR ν 3440, 3340, 1725, 690; 1H NMR (200 MHz) δ 3.96 (br s, 4 H, $2 \times CH_2Ph$), 4.49 (d, $J = 5.5$ Hz, 2 H, OCH_2), 5.12-5.19 (m, 2 H, $=CH_2$), 5.73-5.92 (m, 2 H, $=CH$ and NH), 7.24-7.32 (m, 10 H, ArH); Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.75; N, 9.54.

1-Benzyl-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-2-hydrazinecarboxylic acid allyl ester (20). According to the general procedure A, **12** (3.42 g, 16.6 mmol) was alkylated by using 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (2.97 g, 18.3 mmol) and K_2CO_3 (2.52 g, 18.3 mmol) in 2-butanone (175 mL).

Work-up and fc (ethyl acetate/hexane 1:4) afforded **20** (3.20 g, 9.60 mmol, 58%) as a colorless oil, R_f 0.55. IR ν 3440, 3340, 1720, 1240, 850, 690; ^1H NMR (200 MHz) δ -0.04 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 1.69 (s, 2 H, CH_2Si), 3.35 (br s, 2 H, NCH_2), 4.03 (br s, 2 H, CH_2Ph), 4.53 (d, $J = 5.2$ Hz, 2 H, OCH_2), 4.68 (s, 1 H, $\text{C}=\text{CHH}$), 4.85 (s, 1 H, $\text{C}=\text{CHH}$), 5.16-5.28 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.75-5.90 (m, 2 H, $=\text{CH}$ and NH), 7.24-7.35 (m, 5 H, ArH).

1-Benzyl-1-[4-(trimethylsilyl)-2-butenyl]-2-hydrazinecarboxylic acid allyl ester (21). According to the general procedure A, **12** (1.40 g, 6.80 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne²⁴ (1.88 g, 7.50 mmol) and K_2CO_3 (1.03 g, 7.50 mmol) in acetone (50 mL) by stirring at rt for 18 h. Work-up and fc (ethyl acetate/hexane 1:6) afforded **21** (1.82 g, 5.50 mmol, 81%) as a colorless oil, R_f 0.35. IR ν 3440, 3340, 2190, 1730, 1240, 850, 690; ^1H NMR (200 MHz) δ 0.16 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 1.56 (t, $J = 2.4$ Hz, 2 H, CH_2Si), 3.60 (t, $J = 2.3$ Hz, 2 H, NCH_2), 3.90 (s, 2 H, CH_2Ph), 4.54 (dt, $J = 5.5, 1.3$ Hz, 2 H, OCH_2), 5.15-5.29 (m, 2 H, $=\text{CH}_2$), 5.77 (m, 2 H, $=\text{CH}$ and NH), 7.26-7.41 (m, 5 H, ArH).

1-Benzyl-1-[(E)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (22). According to the general procedure A, **12** (6.23 g, 30.2 mmol) was alkylated by using (E)-3-bromo-1-(trimethylsilyl)-1-propene (4.09 g, 21.2 mmol) and K_2CO_3 (4.18 g, 30.2 mmol) in 2-butanone (250 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **22** (5.93 g, 18.6 mmol, 88%) as a colorless oil, R_f 0.50. IR ν 3440, 3340, 1740, 1245, 835, 690; ^1H NMR (200 MHz) δ 0.06 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 3.48 (br s, 2 H, NCH_2), 3.98 (br s, 2 H, CH_2Ph), 4.52 (d, $J = 5.0$ Hz, 2 H, OCH_2), 5.15-5.27 (m, 2 H, $=\text{CH}_2$), 5.70-5.91 (m, 2 H, $\text{CH}=\text{CH}_2$, NH and CHSi), 6.12 (dt, $J = 18.6, 5.8$ Hz, 1 H, CH_2CH), 7.27-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(Z)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (23). According to the general procedure A, **12** (3.71 g, 18.0 mmol) was alkylated by using 3-bromo-1-(trimethylsilyl)-1-propene²⁶ (2.31 g, 12.0 mmol, (E)/(Z) 1:2.5) and K_2CO_3 (2.65 g, 19.2 mmol) in 2-butanone (130 mL). Work-up and fc (ethyl acetate/hexane 1:4) afforded **23** (1.97 g, 6.19 mmol, 52%) as a colorless oil, (E)/(Z) 1:1.9, R_f 0.50. IR ν 3440, 3340, 1740, 1245, 835, 690; ^1H NMR (250 MHz) δ 0.07 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 3.55 (br s, 2 H, NCH_2), 4.00 (br s, 2 H, CH_2Ph), 4.52 (d, $J = 4.8$ Hz, 2 H, OCH_2), 5.18-5.28 (m, 2 H, $=\text{CH}_2$), 5.75-5.88 (m, 2 H, $\text{CH}=\text{CH}_2$, NH and CHSi), 6.41 (dt, $J = 14.3, 7.2$ Hz, 1 H, CH_2CH), 7.27-7.35 (m, 5 H, ArH).

General procedure B for the reactions with methyl glyoxylate. To a solution of the hydrazine in toluene was added an excess of freshly distilled methyl glyoxylate at rt.²⁹ After complete reaction (according to TLC), the solution was concentrated *in vacuo*. The residue was taken up in pyridine and treated with an excess of acetic anhydride and a catalytic amount of DMAP. After stirring at rt for 18 h, the dark brown solution was concentrated *in vacuo* and purified by fc to afford the pure product.

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-propenyl)hydrazineacetic acid methyl ester (24). Following the general procedure B, a solution of **13** (3.20 g, 13.0 mmol) in toluene (100 mL) was reacted with methyl glyoxylate (2.29 g, 26.0 mmol) for 4 h and acetylated with Ac_2O (6.15 mL, 65.0 mmol) in pyridine (100 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:5) afforded **24** (4.45 g, 11.8 mmol, 91%) as a colorless oil, R_f 0.45. IR ν 1760, 1740, 1710, 1360, 690; ^1H NMR (200 MHz) δ (some signals appear as rotamers) 1.97, 2.00 (s, 3 H, $\text{C}(\text{O})\text{CH}_3$), 3.50-3.81 (m, 2 H, NCH_2), 3.66, 3.73 (s, 3 H, CO_2CH_3), 4.17-4.25 (m, 2 H, CH_2Ph), 4.68 (br s, 2 H, OCH_2), 4.98-5.34 (m, 4 H, $2 \times =\text{CH}_2$), 5.54-6.03 (m, 2 H, $2 \times =\text{CH}$), 6.55, 6.57 (s, 1 H, NCH), 7.21-7.33 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-methyl-2-propenyl)hydrazineacetic acid methyl ester (25). Following the general procedure B, a solution of **14** (4.00 g, 15.4 mmol) in toluene (150 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 18 h and acetylated with Ac_2O (7.3 mL, 0.08 mol) in pyridine (150 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:5) afforded **25** (5.88 g, 15.1 mmol, 98%) as a colorless oil, R_f 0.30. IR ν 1760, 1740, 1720, 690; ^1H NMR (250 MHz) δ 1.80 (s, 3 H,

CH₃), 1.91 (s, 3 H, C(O)CH₃), 3.41-3.74 (m, 2 H, NCH₂), 3.64 (s, 3 H, CO₂CH₃), 3.95-4.25 (m, 2 H, CH₂Ph), 4.60 (br s, 2 H, OCH₂), 4.80-4.90 (m, 2 H, C=CH₂), 5.10-5.45 (m, 2 H, CH=CH₂), 5.75-6.05 (m, 1 H, =CH), 6.44 (br s, 1 H, NCH), 7.20-7.33 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-methyl-2-butenyl)hydrazineacetic acid methyl ester (26). According to the general procedure B, a solution of 15 (800 mg, 2.90 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.6 g, 29 mmol) for 18 h and acetylated with Ac₂O (2.76 mL, 29 mmol) in pyridine (50 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 26 (670 mg, 1.70 mmol, 57%) as a colorless oil, *R_f* 0.40. IR ν 1760, 1735, 1715, 690; ¹H NMR (250 MHz) δ 1.53-1.73 (m, 6 H, (CH₃)₂C), 1.98 (s, 3 H, C(O)CH₃), 3.40-3.75 (m, 5 H, NCH₂ and CO₂CH₃), 4.10-4.25 (m, 2 H, CH₂Ph), 4.60-4.80 (m, 2 H, OCH₂), 5.15-5.45 (m, 3 H, CH₂ and C=CH), 5.75-6.05 (m, 1 H, CH₂=CH), 6.51 (s, 1 H, NCH), 7.19-7.34 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-butenyl)hydrazineacetic acid methyl ester (27). Following the general procedure B, a solution of 16 (3.00 g, 11.5 mmol) in toluene (120 mL) was reacted with methyl glyoxylate (7.1 g, 80 mmol) for 4 h and acetylated with Ac₂O (7.5 mL, 80 mmol) in pyridine (125 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 27 (3.70 g, 9.5 mmol, 82%) as a colorless oil, *R_f* 0.30. IR ν 1760, 1710, 690; ¹H NMR (300 MHz) δ (some signals appear as rotamers) 1.58, 1.64 (m, 3 H, CH₃), 2.01, 2.05 (s, 3 H, C(O)CH₃), 3.50-3.73 (m, 2 H, NCH₂), 3.66, 3.74 (s, 3 H, CO₂CH₃), 4.10-4.25 (m, 2 H, CH₂Ph), 4.60-4.75 (m, 2 H, OCH₂), 5.23-5.35 (m, 2 H, =CH₂), 5.48-5.57 (m, 2 H, CH=CH), 5.80-6.10 (m, 1 H, CH₂=CH), 6.54 (s, 1 H, NCH), 7.22-7.33 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(ethenylidenemethyl)hydrazineacetic acid methyl ester (28). Following the general procedure B, a solution of 17 (530 mg, 2.10 mmol) in toluene (25 mL) was reacted with methyl glyoxylate (720 mg, 8.2 mmol) for 4 h and acetylated with Ac₂O (0.97 mL, 10.3 mmol) in pyridine (25 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:6) afforded 28 (660 mg, 1.70 mmol, 83%) as a yellow oil, *R_f* 0.40. ¹H NMR δ (some signals appear as rotamers) 2.01 (s, 3 H, C(O)CH₃), 3.48-3.91 (m, 2 H, NCH₂), 3.68, 3.74 (s, 3 H, CO₂CH₃), 4.05-4.40 (m, 2 H, CH₂Ph), 4.55-4.95 (m, 4 H, OCH₂ and C=CH₂), 5.10-5.50 (m, 3 H, CH=CH₂ and C=CH), 5.75-6.10 (m, 1 H, CH₂=CH), 6.57, 6.60 (s, 1 H, NCH), 7.26-7.34 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-butenyl)hydrazineacetic acid methyl ester (29). Following the general procedure B, a solution of 18 (384 mg, 1.48 mmol) in toluene (15 mL) was reacted with methyl glyoxylate (650 mg, 7.4 mmol) for 5 h and acetylated with Ac₂O (0.70 mL, 7.38 mmol) in pyridine (15 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 29 (279 mg, 0.72 mmol, 48%) as a colorless oil, *R_f* 0.45. IR ν 1765, 1740, 1715, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 2.03, 2.06 (s, 3 H, C(O)CH₃), 2.25-2.35 (m, 2 H, NCH₂CH₂), 2.75-3.35 (m, 2 H, NCH₂), 3.70, 3.73 (s, 3 H, CO₂CH₃), 4.10-4.30 (m, 2 H, CH₂Ph), 4.68 (br s, 2 H, OCH₂), 4.88-5.03 (m, 2 H, =CH₂), 5.20-5.45 (m, 2 H, =CH₂), 5.50-6.00 (m, 2 H, 2 \times =CH), 6.54 (s, 1 H, NCH), 7.22-7.40 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2,2-dibenzylhydrazineacetic acid methyl ester (30). According to the general procedure B, a solution of 19 (10.0 g, 33.8 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (5.95 g, 68 mmol) for 40 h and acetylated with Ac₂O (16.0 mL, 169 mmol) in pyridine (200 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 30 (14.3 g, 33.6 mmol, 99%) as a colorless oil, *R_f* 0.30. IR ν 1760, 1735, 1715, 1220, 690; ¹H NMR (200 MHz) δ 1.77 (br s, 3 H, C(O)CH₃), 3.57 (s, 3 H, CO₂CH₃), 4.10-4.41 (m, 4 H, 2 \times CH₂Ph), 4.69 (br s, 2 H, OCH₂), 5.15-5.40 (m, 2 H, =CH₂), 5.60-6.10 (m, 1 H, =CH), 6.42 (s, 1 H, NCH), 7.21-7.37 (m, 10 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-{2-[(trimethylsilyl)methyl]-2-propenyl}hydrazineacetic acid methyl ester (31). Following the general procedure B, a solution of 20 (1.00 g, 3.01 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.65 g, 30.1 mmol) for 18 h (2 \times)

and acetylated with Ac_2O (1.42 mL, 15.1 mmol) in pyridine (30 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **31** (1.10 g, 2.38 mmol, 79%) as a colorless oil, R_f 0.50. IR ν 1760, 1735, 1715, 1240, 850, 690; ^1H NMR (200 MHz) δ (some signals appear as rotamers) -0.10, -0.09 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 1.43, 1.63 (s, 2 H, CH_2Si), 1.91 (s, 3 H, $\text{C}(\text{O})\text{CH}_3$), 3.25-3.70 (m, 2 H, NCH_2), 3.66 (s, 3 H, CO_2CH_3), 3.85-4.35 (m, 2 H, CH_2Ph), 4.50-4.75 (m, 3 H, OCH_2 and $\text{C}=\text{CHH}$), 4.88 (s, 1 H, $\text{C}=\text{CHH}$), 5.15-5.50 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.75-6.10 (m, 1 H, $=\text{CH}$), 6.42 (s, 1 H, NCH), 7.22-7.34 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[4-(trimethylsilyl)-2-butynyl]hydrazineacetic acid methyl ester (32). According to the general procedure B, a solution of **21** (150 mg, 0.45 mmol) in toluene (5 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 4 h at 80 °C and acetylated with Ac_2O (220 μL , 2.27 mmol) in pyridine (5 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:6) afforded **32** (170 mg, 0.37 mmol, 82%) as a light yellow oil, R_f 0.35. IR ν 2210, 1765, 1735, 1715, 1245, 845, 690; ^1H NMR δ (some signals appear as rotamers) 0.08, 0.09 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 1.40-1.55 (m, 2 H, CH_2Si), 1.75-2.00 (m, 3 H, $\text{C}(\text{O})\text{CH}_3$), 3.55-3.95 (m, 5 H, NCH_2 and CO_2CH_3), 4.24 (br s, 2 H, CH_2Ph), 4.66 (m, 2 H, OCH_2), 5.15-5.36 (m, 2 H, $=\text{CH}_2$), 5.82-5.96 (m, 1 H, $=\text{CH}$), 6.50 (s, 1 H, NCH), 7.26-7.37 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(*E*)-3-(trimethylsilyl)-2-propenyl]hydrazineacetic acid methyl ester (33). Following the general procedure B, a solution of **22** (5.93 g, 18.6 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (13.1 g, 150 mmol) for 42 h and acetylated with Ac_2O (17.6 mL, 0.19 mol) in pyridine (200 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:3) afforded **33** (6.20 g, 13.8 mmol, 74%) as a light yellow oil, R_f 0.50. IR ν 1765, 1700, 1240, 840, 690; ^1H NMR (200 MHz) δ (some signals appear as rotamers) -0.06, 0.00 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 2.00, 2.05 (s, 3 H, $\text{C}(\text{O})\text{CH}_3$), 3.68 (br s, 2 H, NCH_2), 3.75 (s, 3 H, CO_2CH_3), 4.05-4.25 (m, 2 H, CH_2Ph), 4.55-4.80 (m, 2 H, OCH_2), 5.15-5.50 (m, 2 H, $=\text{CH}_2$), 5.68-5.77 (m, 2 H, $\text{CH}=\text{CH}$), 5.80-6.15 (m, 1 H, $\text{CH}_2=\text{CH}$), 6.50, 6.60 (s, 1 H, NCH), 7.24-7.32 (m, 5 H, ArH).

α -Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(*Z*)-3-(trimethylsilyl)-2-propenyl]hydrazineacetic acid methyl ester (34). Following the general procedure B, a solution of **23** (1.95 g, 6.13 mmol) in toluene (60 mL) was reacted with methyl glyoxylate (2.70 g, 30.7 mmol) for 42 h and acetylated with Ac_2O (5.8 mL, 61 mmol) in pyridine (60 mL). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **34** (2.17 g, 4.84 mmol, 79%) as a light yellow oil, (*E*)/(*Z*) 1:1.2, R_f 0.50. IR ν 1760, 1740, 1720, 1240, 835, 690; ^1H NMR (250 MHz) δ 0.05 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 1.94 (s, 3 H, $\text{C}(\text{O})\text{CH}_3$), 3.64 (br s, 2 H, NCH_2), 3.70 (s, 3 H, CO_2CH_3), 4.05-4.22 (m, 2 H, CH_2Ph), 4.65-4.75 (m, 2 H, OCH_2), 5.15-5.35 (m, 2 H, $=\text{CH}_2$), 5.40-6.00 (m, 2 H, CHSi and $=\text{CH}$), 6.42 (dt, $J = 14.3, 7.2$ Hz, 1 H, CH_2CH), 6.63 (s, 1 H, NCH), 7.22-7.32 (m, 5 H, ArH).

General procedure C for the cyclization reactions with Lewis acids. To a 0.1 M solution of the hydrazide in CH_2Cl_2 was added TiCl_4 , SnCl_4 (2 equiv of a solution in CH_2Cl_2) or Et_2AlCl (2 equiv of a 1.0 M solution in toluene) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq satd NaHCO_3 and the resulting suspension was filtered over Celite and extracted with CH_2Cl_2 (3 \times). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification of the residue by fc afforded the pure cyclization product(s).

***rel*-(3*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (*trans*-35).** According to the general procedure C, a solution of **24** (500 mg, 1.33 mmol) in CH_2Cl_2 (13 mL) was cyclized by using SnCl_4 (1.33 mL of a 2.0 M solution, 2.66 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded **35** (352 mg, 1.00 mmol, 75%) as a colorless oil, *c/tr* 1:5, R_f 0.25. *trans*-35: IR ν 1740, 1680, 1375, 690; ^1H NMR δ 2.46-2.72 (m, 2 H, $2 \times \text{H}_4$), 3.11 (dd, $J = 8.8, 10.6$ Hz, 1 H, CHHCl), 3.31-3.44 (m, 2 H, CHHCl and H_5), 3.80 (d, $J = 12.6$ Hz, 1 H, CHHPh), 3.81 (s, 3 H, CO_2CH_3),

4.24 (d, $J = 12.6$ Hz, 1 H, CHHPh), 4.50–4.60 (m, 2 H, OCH₂), 4.67 (t, $J = 8.8$ Hz, 1 H, H3), 5.17–5.35 (m, 2 H, =CH₂), 5.79–5.97 (m, 1 H, =CH), 7.27–7.47 (m, 5 H, ArH); ¹³C NMR (50 MHz) δ 31.9 (C4), 45.0 (CH₂Cl), 52.6 (CO₂CH₃), 59.4 (C3), 62.1 (CH₂Ph), 64.1 (C5), 66.4 (OCH₂), 117.5 (=CH₂), 127.7, 128.4, 129.4 (ArH), 132.5 (=CH), 137.0 (ArC), 172.6 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 352 (M^+ , 90), 267 (55), 217 (52), 91 (100); HRMS calcd for C₁₇H₂₁N₂O₄ 354.1160, found 354.1171. *cis*-35: ¹³C NMR (50 MHz) δ 31.3 (C4), 44.5 (CH₂Cl), 52.4 (CO₂CH₃), 58.6 (C3), 60.6 (CH₂Ph), 64.0 (C5), 66.4 (OCH₂), 117.7 (=CH₂), 127.8, 128.4, 129.4 (ArH), 132.4 (=CH), 136.2 (ArC), 171.6 (C(O)).

Cyclization of 25 with Et₂AlCl. Following the general procedure C, a solution of 25 (982 mg, 2.52 mmol) in CH₂Cl₂ (25 mL) was treated with Et₂AlCl (7.55 mL of a 1.0 M solution in toluene, 7.55 mmol). Work-up and fc (ethyl acetate/hexane 1:5) afforded *rel*-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-chloro-5-methylhexahydro-3-pyridazinecarboxylic acid methyl ester (*trans*-37) (488 mg, 1.33 mmol, 53%) as a colorless oil, *rel*-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (*trans*-36) (178 mg, 0.49 mmol, 19%) as an inseparable mixture with *cis*-37 (59 mg, 0.16 mmol, 6%) and *cis*-36 (76 mg, 0.21 mmol, 8%) as a colorless oil, R_f 0.20. *trans*-37: IR ν 1735, 1700, 690; ¹H NMR (200 MHz) δ 1.51 (s, 3 H, CH₃), 2.35 (br s, 2 H, H4), 2.86 (d, $J = 13.5$ Hz, 1 H, H6), 3.20 (d, $J = 13.5$ Hz, 1 H, H6), 3.76 (s, 3 H, CO₂CH₃), 4.30 (d, $J = 14.0$ Hz, 1 H, CHHPh), 4.41 (d, $J = 14.0$ Hz, 1 H, CHHPh), 4.63–4.65 (m, 2 H, OCH₂), 4.70–4.90 (m, 1 H, H3), 5.22–5.36 (m, 2 H, =CH₂), 5.68–6.05 (m, 1 H, =CH), 7.26–7.40 (m, 5 H, ArH); ¹³C NMR (50 MHz) δ 30.6 (CH₃), 40.0 (C4), 52.3 (CO₂CH₃), 52.5 (C3), 60.2 (CH₂Ph), 66.8 (OCH₂), 118.3 (=CH₂), 127.8, 128.2, 129.2 (ArH), 132.2 (=CH), 137.7 (ArC); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 6), 331 (14), 281 (8), 231 (5), 160 (41), 91 (100); HRMS calcd for C₁₈H₂₃N₂O₄Cl 366.1346, found 366.1318. *cis*-37: ¹H NMR (300 MHz) δ 1.30 (s, 3 H, CH₃), 2.06 (dd, $J = 14.6, 7.2$ Hz, 1 H, H4), 2.86–2.88 (m, 2 H, H4 and H6), 3.02 (d, $J = 14.7$ Hz, 1 H, H6), 3.82 (s, 3 H, CO₂CH₃), 4.01 (d, $J = 13.0$ Hz, 1 H, CHHPh), 4.10 (d, $J = 13.0$ Hz, 1 H, CHHPh), 4.15–4.90 (m, 3 H, OCH₂ and H3), 4.95–5.40 (m, 2 H, =CH₂), 5.92–6.03 (m, 1 H, =CH), 7.20–7.52 (m, 5 H, ArH); ¹³C NMR (50 MHz) δ 30.8 (CH₃), 40.0 (C4), 52.3 (CO₂CH₃), 57.9 (CH₂Ph), 59.6 (C6), 59.7 (C3), 63.0 (C5), 67.0 (OCH₂), 117.6 (=CH₂), 127.2, 128.2, 129.6 (ArH), 132.5 (=CH), 138.1 (ArC), 172.6 (C(O)). *trans*-36: IR ν 1745, 1685, 690; ¹H NMR (200 MHz) δ 1.43 (s, 3 H, CH₃), 2.19 (dd, $J = 13.2$ Hz, 10.6 Hz, 1 H, H4), 2.88 (dd, $J = 13.2, 8.9$ Hz, 1 H, H4), 3.18 (d, $J = 11.3$ Hz, 1 H, CHHCl), 3.37 (d, $J = 11.3, 1$ H, CHHCl), 3.82 (s, 3 H, CO₂CH₃), 4.00 (d, $J = 13.2$ Hz, 1 H, CHHPh), 4.11 (d, $J = 13.2$ Hz, 1 H, NCHHPh), 4.41–4.55 (m, 3 H, H3 and OCH₂), 5.10–5.23 (m, 2 H, =CH₂), 5.55–5.80 (m, 1 H, =CH), 7.22–7.53 (m, 5 H, ArH); ¹³C NMR (63 MHz) δ 19.7 (CH₃), 37.1 (C4), 49.2 (CH₂Cl), 52.5 (CO₂CH₃), 58.1 (CH₂Ph), 59.6 (C3), 66.4 (C9), 69.3 (C5), 118.2 (=CH₂), 127.0, 128.0, 129.4 (ArH), 132.3 (=CH), 138.0 (ArC), 172.6 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 45), 331 (31), 317 (14), 281 (18), 231 (31), 91 (100); HRMS calcd for C₁₈H₂₃N₂O₄Cl 366.1346, found 366.1381. *cis*-36: IR ν 1745, 1685, 690; ¹H NMR (200 MHz) δ 1.27 (s, 3 H, CH₃), 2.37–2.43 (m, 2 H, 2 \times H4), 3.51 (d, $J = 11.2$ Hz, 1 H, CHHCl), 3.76 (d, $J = 11.2$ Hz, 1 H, CHHCl), 3.79 (s, 3 H, CO₂CH₃), 3.96 (s, 2 H, CH₂Ph), 4.25–4.45 (m, 2 H, OCH₂), 4.50–4.70 (m, 1 H, H3), 5.09–5.21 (m, 2 H, =CH₂), 5.55–5.80 (m, 1 H, =CH), 7.24–7.49 (m, 5 H, ArH); ¹H NMR (250 MHz, 50 °C) δ 1.25 (s, 3 H, CH₃), 2.30–2.44 (m, 2 H, 2 \times H4), 3.47 (d, $J = 11.3$ Hz, 1 H, CHHCl), 3.73 (d, $J = 11.3$ Hz, 1 H, CHHCl), 3.78 (s, 3 H, CO₂CH₃), 3.97 (s, 2 H, CH₂Ph), 4.25–4.45 (m, 2 H, OCH₂), 4.57 (dd, $J = 9.1, 7.7$ Hz, 1 H, H3), 5.08–5.20 (m, 2 H, =CH₂), 5.60–5.80 (m, 1 H, =CH), 7.18–7.47 (m, 5 H, ArH); ¹³C NMR (50 MHz) δ 22.3 (CH₃), 38.4 (C4), 48.8 (CH₂Cl), 52.5 (CO₂CH₃), 56.9 (CH₂Ph), 59.5 (C3), 66.3 (OCH₂), 68.4 (C5), 117.4 (=CH₂), 127.2, 128.0, 129.6 (ArH), 132.4 (=CH), 137.3 (ArC), 173.1 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 68), 331 (10), 317 (20), 307 (6), 281 (35), 255 (9), 231 (59), 91 (100); HRMS calcd for C₁₈H₂₃N₂O₄Cl 366.1346, found 366.1387.

***rel*-(3*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-formyloxy-5-methylhexahydro-3-pyridazinecarboxylic acid methyl ester (38).** A solution of 25 (565 mg, 1.45 mmol) in HCOOH (15 mL) was stirred for 18 h at rt. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 38 (369 mg,

0.98 mmol, 68%) as a colorless oil, R_f 0.30. IR ν 1740, 1700, 690; ^1H NMR (200 MHz) δ 1.51 (s, 3 H, CH_3), 2.20–2.40 (m, 1 H, H4), 2.40–2.60 (m, 1 H, H4), 2.87 (d, $J = 13.7$ Hz, 1 H, H6), 3.38 (d, $J = 13.7$ Hz, 1 H, H6), 3.74 (s, 3 H, CO_2CH_3), 4.20 (d, $J = 13.7$ Hz, 1 H, CH_2Ph), 4.27 (d, $J = 13.7$ Hz, 1 H, CH_2Ph), 4.64 (d, $J = 5.5$ Hz, 2 H, OCH_2 and br s, 1 H, H3), 5.22–5.36 (m, 2 H, $=\text{CH}_2$), 5.80–6.05 (m, 1 H, $=\text{CH}$), 7.22–7.33 (m, 5 H, ArH), 7.91 (s, 1 H, CHO); ^{13}C NMR (50 MHz) δ 24.4 (CH_3), 34.9 (C4), 52.2 (CO_2CH_3), 54.5 (C3), 56.7 (CH_2Ph), 61.0 (C6), 66.6 (OCH_2), 79.4 (C5), 118.1 ($=\text{CH}_2$), 127.3, 128.1, 128.9 (ArH), 132.2 ($=\text{CH}$), 137.6 (ArC), 157.0, 159.7, 172.0 ($3 \times \text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 376 (M^+ , 43), 331 (14), 317 (7), 259 (13), 245 (26), 91 (100); HRMS calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_6\text{Cl}$ 376.1634, found 376.1609.

rel-(3*S*,4*S*)-2-(Allyloxycarbonyl)-1-benzyl-4-(1-chloromethylethyl)-3-pyrazolidinecarboxylic acid methyl ester (39). Following the general procedure C, a solution of 26 (140 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) was treated with SnCl_4 (0.58 mL of a 1.2 M solution, 0.70 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 39 (76 mg, 0.20 mmol, 58%) as a colorless oil, R_f 0.25. IR ν 1735, 1690, 690; ^1H NMR (200 MHz) δ 1.54 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 3.13–3.28 (m, 3 H, H4 and $2 \times \text{H}5$), 3.81 (d, $J = 12.5$ Hz, 1 H, CHHPh), 3.82 (s, 3 H, CO_2CH_3), 4.17 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.56 (d, $J = 5.3$ Hz, 2 H, OCH_2), 4.70 (d, $J = 6.2$ Hz, 1 H, H3), 5.15–5.31 (m, 2 H, $=\text{CH}_2$), 5.70–5.95 (m, 1 H, $=\text{CH}$), 7.26–7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 31.5, 31.9 ($2 \times \text{CH}_3$), 52.7 (CO_2CH_3), 54.9 (C5), 55.8 (C4), 61.9 (CH_2Ph), 62.6 (C3), 66.5 (OCH_2), 69.4 (CCl), 117.6 ($=\text{CH}_2$), 127.5, 128.2, 129.4 (ArH), 132.3 ($=\text{CH}$), 137.2 (ArC), 173.4 ($\text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 380 (M^+ , 67), 344 (36), 295 (44), 245 (51), 91 (100); HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4\text{Cl}$ 380.1503, found 380.1548.

rel-(3*S*,4*S*)-2-(allyloxycarbonyl)-1-benzyl-4-[1-(formyloxy)-1-methylethyl]-3-pyrazolidinecarboxylic acid methyl ester (40). A solution of 26 (173 mg, 0.43 mmol) in HCOOH (5 mL) was stirred at rt for 18 h. Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 40 (110 mg, 0.28 mmol, 66%) as a colorless oil, R_f 0.25. IR ν 1735, 1715, 1690, 690; ^1H NMR (200 MHz) δ 1.53 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 3.06 (d, $J = 8.7$ Hz, 2 H, $2 \times \text{H}5$), 3.26–3.39 (m, 1 H, H4), 3.81 (s, 3 H, CO_2CH_3), 3.82 (d, $J = 12.3$ Hz, 1 H, CHHPh), 4.20 (d, $J = 12.3$ Hz, 1 H, CHHPh), 4.56 (d, $J = 5.5$ Hz, 2 H, OCH_2), 4.62 (d, $J = 7.4$ Hz, 1 H, H3), 5.16–5.32 (m, 2 H, $=\text{CH}_2$), 5.75–5.95 (m, 1 H, $=\text{CH}$), 7.27–7.43 (m, 5 H, ArH), 7.93 (s, 1 H, OCHO); ^{13}C NMR (50 MHz) δ 24.2, 25.0 ($2 \times \text{CH}_3$), 52.6 (CO_2CH_3), 53.3 (C5), 53.7 (C4), 61.3 (C3), 61.7 (CH_2Ph), 66.5 (OCH_2), 81.6 (CO), 117.7 ($=\text{CH}_2$), 127.4, 128.2, 129.4 (ArH), 132.3 ($=\text{CH}$), 137.1 (ArC), 159.8, 173.2 ($2 \times \text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 390 (M^+ , 34), 345 (6), 227 (20), 91 (100); HRMS calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6$ 390.1791, found 390.1749.

rel-(3*S*,4*S*)-2-(Allyloxycarbonyl)-1-benzyl-4-(1-chloroethyl)-3-pyrazolidinecarboxylic acid methyl ester (41). According to the general procedure C, a solution of 27 (513 mg, 1.32 mmol) in CH_2Cl_2 (15 mL) was treated with SnCl_4 (2.19 mL of a 1.2 M solution, 2.63 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 41 (267 mg, 0.73 mmol, 56%) as a colorless oil, 1:5 mixture of isomers, R_f 0.30. IR ν 1740, 1690, 690; ^1H NMR (250 MHz) δ (mixture) 1.57 (d, $J = 6.4$ Hz, 3 H, CH_3), 3.05–3.17 (m, 3 H, H4 and $2 \times \text{H}5$), 3.72–3.82 (m, 1 H, CHHPh), 3.80 (s, 3 H, CO_2CH_3), 4.16 (d, $J = 12.4$ Hz, 1 H, CHHPh), 4.24–4.28 (m, 1 H, H3), 4.46–4.53 (m, 3 H, CHCl and OCH_2), 5.13–5.27 (m, 2 H, $=\text{CH}_2$), 5.72–5.90 (m, 1 H, $=\text{CH}$), 7.24–7.43 (m, 5 H, ArH); ^1H NMR (250 MHz, 50 °C) δ 1.56 (d, $J = 6.7$ Hz, 3 H, CH_3), 3.05–3.18 (m, 3 H, H4 and $2 \times \text{H}5$), 3.76 (d, $J = 12.3$ Hz, 1 H, CHHPh), 3.81 (s, 3 H, CO_2CH_3), 4.19 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.25–4.27 (m, 1 H, H3), 4.48–4.50 (m, 1 H, CHCl), 4.55 (d, $J = 5.5$ Hz, 2 H, OCH_2), 5.14–5.29 (m, 2 H, $=\text{CH}_2$), 5.72–5.95 (m, 1 H, $=\text{CH}$), 7.22–7.43 (m, 5 H, ArH); ^{13}C NMR (63 MHz) δ (mixture) 23.5, 24.1 (CH_3), 51.5, 51.8 (C4), 52.5, 52.7 (CO_2CH_3), 54.6, 55.3 (C5), 57.5, 56.8 (CHCl), 61.7, 62.0 (CH_2Ph), 63.2, 63.0 (C3), 66.6, 66.7 (OCH_2), 117.7, 118.3 ($=\text{CH}_2$), 127.5, 127.7, 128.3, 128.4, 129.5, 129.8 (ArH), 132.2, 132.3 ($=\text{CH}$), 137.1, 137.2 (ArC), 154.2, 154.3, 172.4, 172.5 ($2 \times \text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 38), 330 (6), 281 (21), 231 (24), 91 (100); HRMS calcd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_4\text{Cl}$ 366.1346, found 366.1369.

2-(Allyloxycarbonyl)-1-benzyl-4-[(chloromethyl)methylene]-3-pyrazolidinecarboxylic acid methyl ester (42). According to the general procedure C, a solution of 28 (660 mg, 1.70 mmol) in CH_2Cl_2 (17 mL) was treated with TiCl_4 (2.84 mL of a 1.2 M solution, 3.40 mmol). Work-up and fc (ethyl acetate/hexane 1:6) afforded 42 (280 mg, 0.77 mmol, 45%) as a yellowish oil, 1.2:1 mixture of two isomers, R_f 0.40. IR ν 1740, 1700, 690; ^1H NMR (200 MHz) δ (one isomer) 2.61–2.75 (m, 1 H, CHHCl), 3.31 (dd, $J = 6.4, 3.1$ Hz, 1 H, CHHCl), 3.55–4.00 (m, 2 H, $2 \times \text{H5}$), 3.71 (s, 3 H, CO_2CH_3), 4.35 (d, $J = 13.4$ Hz, 1 H, CHHPh), 4.47 (d, $J = 13.4$ Hz, 1 H, CHHPh), 4.65 (m, 2 H, OCH_2), 4.90 (dd, $J = 12.2, 5.4$ Hz, 1 H, C=CH), 5.21–5.45 (m, 2 H, $=\text{CH}_2$), 5.56–5.60 (br s, 1 H, H3), 5.83–6.10 (m, 1 H, $\text{CH}_2=\text{CH}$), 7.26–7.41 (m, 5 H, ArH); (other isomer) 2.61–2.75 (m, 1 H, CHHCl), 3.25 (dd, $J = 6.5, 3.1$ Hz, 1 H, CHHCl), 3.55–4.00 (m, 2 H, $2 \times \text{H5}$), 3.71 (s, 3 H, CO_2CH_3), 4.11 (d, $J = 13.4$ Hz, 1 H, CHHPh), 4.46 (d, $J = 13.4$ Hz, 1 H, CHHPh), 4.77 (d, $J = 5.7$ Hz, 2 H, OCH_2), 5.05 (dd, $J = 12.6, 5.4$ Hz, 1 H, C=CH), 5.21–5.45 (m, 2 H, $=\text{CH}_2$), 5.56–5.60 (br s, 1 H, H3), 5.83–6.10 (m, 1 H, $\text{CH}_2=\text{CH}$), 7.26–7.41 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (mixture) 36.5, 36.6 (CH_2Cl), 51.2, 51.8 (C5), 52.4, 52.5 (CO_2CH_3), 59.9, 60.9 (CH_2Ph), 60.8, 61.1 (C3), 66.1, 66.9 (OCH_2), 117.3, 118.5 ($=\text{CH}_2$), 124.9, 125.7 (C=CH), 127.0, 127.3 (C4), 127.5, 128.4, 128.9 (ArH), 132.3, 132.4 ($\text{CH}_2=\text{CH}$), 138.2, 138.3 (ArC), 154.5, 171.3, 171.4 ($2 \times \text{C(O)}$); MS (EI, 70 eV), m/z (relative intensity) 364 (M^+ , 6), 329 (25), 305 (11), 273 (42), 193 (21), 91 (100); HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_4\text{Cl}$ 364.1190, found 364.1159.

2-(Allyloxycarbonyl)-1-benzyl-5-chloro-1H-1,2-diazepine-3-carboxylic acid methyl ester (43). Following the general procedure C, a solution of 29 (279 mg, 0.72 mmol) in CH_2Cl_2 (7 mL) was treated with SnCl_4 (1.19 mL of a 1.2 M solution, 1.43 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 43 (170 mg, 0.46 mmol, 65%) as a colorless oil, 1:1 mixture of isomers, R_f 0.25. IR ν 1745, 1685, 690; ^1H NMR (200 MHz) δ (mixture) 1.50–1.75 (m, 2 H, $2 \times \text{H6}$), 2.23 (dd, $J = 12.7, 9.0$ Hz, 1 H, H4), 2.61 (ddd, $J = 13.0, 9.2, 7.2$ Hz, 1 H, H4), 3.15–3.50 (m, 3 H, $2 \times \text{H7}$ and H5), 3.73 (d, $J = 12.4$ Hz, 1 H, CHHPh), 3.81 (s, 3 H, CO_2CH_3), 4.17 (d, $J = 12.4$ Hz, 1 H, CHHPh), 4.48–4.67 (m, 3 H, OCH_2 and H3), 5.18–5.33 (m, 2 H, $=\text{CH}_2$), 5.77–5.94 (m, 1 H, $=\text{CH}$), 7.26–7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (mixture) 30.4, 34.3, 35.9, 36.0 (C4 and C6), 41.9 (C7), 52.6 (CO_2CH_3), 59.6 (C3), 59.2, 61.2 (C5), 61.6 (CH_2Ph), 66.3 (OCH_2), 117.5 ($=\text{CH}_2$), 127.3, 128.1, 129.5 (ArH), 132.2 ($=\text{CH}$), 137.0 (ArC), 172.7 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 52), 325 (9), 303 (6), 275 (23), 91 (100).

2-(Allyloxycarbonyl)-3-benzyl-1,2,3,4-tetrahydro-1-phthalazinecarboxylic acid methyl ester (44). According to the general procedure C, a solution of 30 (2.00 g, 4.69 mmol) in CH_2Cl_2 (45 mL) was treated with SnCl_4 (7.82 mL of a 1.2 M solution, 9.38 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 44 (1.55 mg, 4.23 mmol, 91%) as a colorless oil, R_f 0.30. IR ν 1740, 1685, 1400, 690; ^1H NMR δ 3.65–3.75 (m, 2 H, NCH_2), 3.78 (br s, 3 H, CO_2CH_3), 3.95–4.20 (m, 1 H, CHHPh), 4.45–4.70 (m, 3 H, OCH_2 and CHHPh), 5.15–5.40 (m, 2 H, $=\text{CH}_2$), 5.63 (br s, 1 H, NCH), 5.80–6.05 (m, 1 H, $=\text{CH}$), 7.00–7.50 (m, 9 H, ArH); ^{13}C NMR (50 MHz) δ 51.5 (NCH), 52.6 (CO_2CH_3), 57.7 (NCH_2), 59.3 (CH_2Ph), 66.7 (OCH_2), 117.9 ($=\text{CH}_2$), 118.6, 127.1, 127.5, 128.3, 128.8, 129.3 (ArH), 132.5 ($=\text{CH}$), 134.0, 135.1, 137.0 (ArC), 171.0 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 366 (M^+ , 32), 307 (15), 226 (32), 105 (100), 91 (100); HRMS calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$ 366.1580, found 366.1579.

2-(Allyloxycarbonyl)-1-benzyl-5-methylenehexahydro-3-pyridazinecarboxylic acid methyl ester (45). According to the general procedure C, a solution of 31 (1.10 g, 2.38 mmol) in CH_2Cl_2 (25 mL) was treated with Et_2AlCl (5.95 mL of a 1.0 M solution, 5.95 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 45 (517 mg, 1.57 mmol, 83% (after correction)) as a colorless oil, R_f 0.35. IR ν 1735, 1680, 690; ^1H NMR (200 MHz) δ 2.59–2.70 (m, 1 H, H4), 3.01 (d, $J = 14.1$ Hz, 1 H, H4), 3.20 (m, 1 H, H6), 3.40 (d, $J = 14.3$ Hz, 1 H, H6), 3.75 (s, 3 H, CO_2CH_3), 3.86 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.05 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.62–4.80 (m, 2 H, OCH_2), 4.88 (s, 1 H, C=CHH), 5.05 (m, 1 H, H3), 5.15 (s, 1 H, C=CHH), 5.24–5.43 (m, 2 H, CH=CH_2), 5.96–6.04 (m, 1 H, $=\text{CH}$), 7.23–7.40 (m, 5 H, ArH); ^1H NMR (250 MHz, 50 $^\circ\text{C}$) δ 2.64 (dd, $J = 14.2, 7.4$ Hz, 1 H, H4), 2.96 (dd, $J = 14.2, 3.3$ Hz, 1 H, H4), 3.21 (d, $J = 14.5$ Hz, 1 H,

H6), 3.42 (d, $J = 14.5$ Hz, 1 H, H6), 3.73 (s, 3 H, CO_2CH_3), 3.91 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.08 (d, $J = 12.5$ Hz, 1 H, NCHHPh), 4.65–4.80 (m, 2 H, OCH_2), 4.84 (s, 1 H, $\text{C}=\text{CHH}$), 4.97 (br s, 1 H, H3), 5.10 (s, 1 H, $\text{C}=\text{CHH}$), 5.22–5.40 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.91–6.07 (m, 1 H, $=\text{CH}$), 7.20–7.39 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 32.0 (C4), 52.2 (CO_2CH_3), 53.9 (C6), 55.5 (C3), 57.9 (CH_2Ph), 66.6 (OCH_2), 91.5 (C5), 113.7 ($\text{C}=\text{CH}_2$), 117.6 ($\text{CH}=\text{CH}_2$), 127.2, 128.1, 129.0 (ArH), 132.5 ($=\text{CH}$), 137.4 (ArC), 172.0 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 330 (M^+ , 46), 271 (24), 245 (44), 195 (20), 185 (24), 159 (69), 142 (29), 135 (42), 91 (100); HRMS calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ 330.1580, found 330.1548.

rel-(3*S*,5*S*)-2-(allyloxycarbonyl)-1-benzyl-5-methyl-5-(trifluoroacetoxy)hexahydro-3-pyridazinecarboxylic acid methyl ester (46). A solution of 31 (232 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was treated with $\text{CF}_3\text{CO}_2\text{H}$ (155 μL , 2.00 mmol) at 0 °C. After being stirred at rt for 18 h, the mixture was poured into aq satd NaHCO_3 (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:4) to afford 46 (155 mg, 0.35 mmol, 70%) as a light yellow oil, R_f 0.35. IR ν 1775, 1735, 1710, 690; ^1H NMR (200 MHz) δ 1.54 (s, 3 H, CH_3), 2.30–2.55 (m, 2 H, $2 \times \text{H}_4$), 2.89 (d, $J = 13.7$ Hz, 1 H, H6), 3.39 (d, $J = 13.7$ Hz, 1 H, H6), 3.76 (s, 3 H, CO_2CH_3), 4.27 (s, 2 H, CH_2Ph), 4.65 (d, $J = 5.5$ Hz, 2 H, OCH_2), 4.75–4.95 (m, 1 H, H3), 5.24–5.37 (m, 2 H, $=\text{CH}_2$), 5.80–6.05 (m, 1 H, $=\text{CH}$), 7.26–7.34 (m, 5 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 444 (M^+ , 8), 348 (13), 277 (8), 263 (7), 245 (10), 160 (42), 121 (29), 91 (100); HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_6\text{F}_3$ 444.1508, found 444.1543.

2-(Allyloxycarbonyl)-1-benzyl-4-ethenylidene-3-pyrazolidinecarboxylic acid methyl ester (47). To a solution of 32 (250 mg, 0.53 mmol) in CH_2Cl_2 (25 mL) was added at 0 °C $\text{BF}_3 \cdot \text{OEt}_2$ (0.40 mL, 3.15 mmol) and the mixture was stirred at 0 °C for 15 min. After stirring at rt for 4 h, the mixture was poured into aq satd NaCl (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (MgSO_4), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:5) to afford 47 (51 mg, 0.16 mmol, 30% (after correction)) as a light yellow oil, R_f 0.20. IR ν 1950, 1745, 1685, 690; ^1H NMR (200 MHz) δ 3.65 (m, 2 H, $2 \times \text{H}_5$), 3.81 (s, 3 H, CO_2CH_3), 3.83 (d, $J = 12.4$ Hz, 1 H, CHHPh), 4.10 (d, $J = 12.4$ Hz, 1 H, CHHPh), 4.59 (d, $J = 5.5$ Hz, 2 H, OCH_2), 4.65–4.75 (m, 1 H, H3), 5.08–5.11 (m, 2 H, $\text{C}=\text{CH}_2$), 5.18–5.34 (m, 2 H, $\text{CH}=\text{CH}_2$), 5.77–5.97 (m, 1 H, $=\text{CH}$), 7.28–7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 52.6 (CO_2CH_3), 55.5 (C5), 61.3 (C3), 61.8 (CH_2Ph), 66.6 (OCH_2), 81.1 ($\text{C}=\text{CH}_2$), 99.0 (C4), 117.9 ($\text{CH}=\text{CH}_2$), 127.6, 128.3, 129.7 (ArH), 132.3 ($=\text{CH}$), 136.8 (ArC), 169.6 (C(O)), 200.3 ($\text{C}=\text{C}=\text{CH}_2$); MS (EI, 70 eV) m/z (relative intensity) 328 (M^+ , 53), 243 (18), 193 (11), 124 (6), 91 (100); HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$ 328.1423, found 328.1401.

rel-(3*R*,4*S*,5*S*)-2-(Allyloxycarbonyl)-1-benzyl-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (48). According to the general procedure C, a solution of 33 (925 mg, 2.06 mmol) in CH_2Cl_2 (25 mL) was treated with SnCl_4 (3.44 mL of a 1.2 M solution, 4.13 mmol). Work-up and fc (ethyl acetate/hexane 1:4) afforded 48 (591 mg, 1.39 mmol, 68%) as a colorless oil, R_f 0.45. IR ν 1735, 1685, 1250, 940, 690; ^1H NMR (200 MHz) δ 0.12 (s, 9 H, $(\text{CH}_3)_3\text{Si}$), 2.00 (t, $J = 9.1$ Hz, 1 H, H4), 3.07 (dd, $J = 11.5, 4.3$ Hz, 1 H, CHHCl), 3.25 (dd, $J = 11.5, 3.4$ Hz, 1 H, CHHCl), 3.47–3.56 (m, 1 H, H5), 3.78 (s, 3 H, CO_2CH_3), 3.99 (d, $J = 12.8$ Hz, 1 H, CHHPh), 4.36 (d, $J = 12.7$ Hz, 1 H, CHHPh), 4.56 (ddt, $J = 13.6, 5.3, 1.4$ Hz, 1 H, OCHH), 4.67 (ddt, $J = 13.6, 5.3, 1.4$ Hz, 1 H, OCHH), 5.01 (d, $J = 9.0$ Hz, 1 H, H3), 5.18–5.40 (m, 2 H, $=\text{CH}_2$), 5.91–5.98 (m, 1 H, $=\text{CH}$), 7.26–7.51 (ArH); ^{13}C NMR (63 MHz) δ 1.5 ($(\text{CH}_3)_3\text{Si}$), 35.3 (C4), 47.7 (CH_2Cl), 52.1 (CO_2CH_3), 62.4 (C3), 63.4 (CH_2Ph), 66.5 (OCH_2), 68.8 (C5), 117.4 ($=\text{CH}_2$), 127.5, 128.2, 129.4 (ArH), 132.6 ($=\text{CH}$), 137.8 (ArC), 156.0, 172.3 ($2 \times \text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 424 (M^+ , 57), 409 (10), 339 (13), 289 (10), 243 (20), 185 (23), 91 (100); HRMS calcd for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_4\text{ClSi}$ 424.1585, found 424.1569.

2-(Allyloxycarbonyl)-1-benzyl-1,2,3,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (49). According to the general procedure C, a solution of 34 (500 mg, 1.12 mmol) in CH_2Cl_2 (12 mL) was

treated with SnCl_4 (1.86 mL of a 1.2 M solution, 2.23 mmol). Work-up and *fc* (ethyl acetate/hexane 1:4) afforded **48** (152 mg, 0.36 mmol, 32%) as a colorless oil, R_f 0.45 and **49** (176 mg, 0.56 mmol, 50%) as a colorless oil, R_f 0.25. **49**: IR ν 1740, 1680, 1400, 985, 690; ^1H NMR (250 MHz) δ 3.09 (dd, $J = 17.6, 4.2$ Hz, 1 H, H6), 3.46 (br d, $J = 19.3$ Hz, 1 H, H6), 3.78 (s, 3 H, CO_2CH_3), 3.82 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.22 (d, $J = 12.5$ Hz, 1 H, CHHPh), 4.60–4.80 (m, 2 H, OCH_2), 5.10 (br s, 1 H, H3), 5.23–5.45 (m, 2 H, $=\text{CH}_2$), 5.65–6.15 (m, 3 H, $\text{CH}_2=\text{CH}$, H4 and H5), 7.22–7.39 (m, 5 H, ArH); ^{13}C NMR (63 MHz) δ 46.9 (C6), 52.4 (CO_2CH_3), 52.5 (C3), 59.3 (CH_2Ph), 66.6 (OCH_2), 117.6 ($=\text{CH}_2$), 121.0, 124.6 (C4 and C5), 127.3, 127.5, 128.0 (ArH), 132.7 ($\text{CH}_2=\text{CH}$), 138.0 (ArC), 155.0, 170.2 ($2 \times \text{C}(\text{O})$); MS (EI, 70 eV) m/z (relative intensity) 316 (M^+ , 10), 257 (10), 231 (13), 171 (14), 91 (100), 41 (43); HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$ 316.1423, found 316.1401.

rel-(3S,5R)-2-(Allyloxycarbonyl)-1-benzyl-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (56). To a refluxing solution of $n\text{-Bu}_3\text{SnH}$ (160 mL, 0.60 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **35** (55 mg, 0.15 mmol) and AIBN (5 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo* and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford **56** (31 mg, 0.097 mmol, 65%) as a colorless oil, R_f 0.25. IR ν 1740, 680, 1400, 690; ^1H NMR (200 MHz) δ 0.98 (d, $J = 7.1$ Hz, 3 H, CH_3), 2.18 (dd, $J = 12.5, 8.7$ Hz, 1 H, H4), 2.45–2.60 (m, 1 H, H4), 3.37 (quintet, $J = 6.6$ Hz, 1 H, H5), 3.74 (d, $J = 12.8$ Hz, 1 H, CHHPh), 3.80 (s, 3 H, CO_2CH_3), 4.17 (d, $J = 12.8$ Hz, 1 H, CHHPh), 4.57 (d, $J = 5.5$ Hz, 2 H, OCH_2), 4.59 (t, $J = 8.9$ Hz, 1 H, H3), 5.14–5.32 (m, 2 H, $=\text{CH}_2$), 5.76–5.95 (m, 1 H, $=\text{CH}$), 7.23–7.47 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 19.9 (CH_3), 35.4 (C4), 52.5 (CO_2CH_3), 58.6, 59.5 ($2 \times \text{NCH}$), 61.5 (CH_2Ph), 66.3 (OCH_2), 117.2 ($=\text{CH}_2$), 127.3, 128.2, 129.4 (ArH), 132.7 ($=\text{CH}$), 137.8 (ArC), 173.2 ($\text{C}(\text{O})$).

2-(Allyloxycarbonyl)-1-benzyl-5,5-dimethyl-3-pyrazolidinecarboxylic acid methyl ester (57). To a refluxing solution of $n\text{-Bu}_3\text{SnH}$ (217 μL , 0.82 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **36** (75 mg, 0.20 mmol) and AIBN (3.4 mg, 0.02 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo* and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford **57** (35 mg, 0.11 mmol, 51%) as a colorless oil, R_f 0.15. IR ν 1740, 1680, 690; ^1H NMR (200 MHz) δ 1.20–1.30 (s, 6 H, $(\text{CH}_3)_2\text{C}$), 2.30 (d, $J = 9.2$ Hz, 2 H, $2 \times \text{H4}$), 3.80 (s, 3 H, CO_2CH_3), 3.85 (d, $J = 12.4$ Hz, 1 H, CHHPh), 3.99 (d, $J = 12.4$ Hz, 1 H, CHHPh), 4.10–4.45 (m, 2 H, OCH_2), 4.60 (t, $J = 9.3$ Hz, 1 H, H3), 5.05–5.17 (m, 2 H, $=\text{CH}_2$), 5.55 (m, 1 H, $=\text{CH}$), 7.17–7.54 (m, 5 H, ArH).

rel-(3S,4S)-2-(Allyloxycarbonyl)-1-benzyl-4-ethyl-3-pyrazolidinecarboxylic acid methyl ester (58). To a refluxing solution of $n\text{-Bu}_3\text{SnH}$ (324 μL , 1.22 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of **41** (112 mg, 0.31 mmol) and AIBN (5.0 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated *in vacuo*, taken up in THF (10 mL) and stirred with KF (93 mg, 1.22 mmol) and TBAF (122 mL of a 1.0 M solution in THF, 0.12 mmol) for 17 h. The organic layer was dried (MgSO_4), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:4) to afford **58** (39 mg, 0.12 mmol, 38%) as a colorless oil, R_f 0.25. IR ν 1740, 1685, 690; ^1H NMR (200 MHz) δ 0.94 (t, $J = 7.5$ Hz, 3 H, CH_2CH_3), 1.40–1.55 (m, 1 H, CHHCH_3), 1.70–1.90 (m, 1 H, CHHCH_3), 2.65–2.73 (m, 2 H, $2 \times \text{H5}$), 3.15–3.18 (m, 1 H, H4), 3.82 (s, 3 H, CO_2CH_3), 3.75–3.85 (m, 1 H, CHHPh), 4.05–4.25 (m, 2 H, CHHPh and H3), 4.53 (d, $J = 5.4$ Hz, 2 H, OCH_2), 5.14–5.30 (m, 2 H, $=\text{CH}_2$), 5.76–5.90 (m, 1 H, $=\text{CH}$), 7.23–7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 12.2 (CH_2CH_3), 24.7 (CH_2CH_3), 45.5 (C4), 52.5 (CO_2CH_3), 57.8 (C5), 61.7 (CH_2Ph), 65.8 (C3), 66.5 (OCH_2), 117.7 ($=\text{CH}_2$), 127.4, 128.3, 129.6 (ArH), 132.5 ($=\text{CH}$), 137.4 (ArC), 173.1 ($\text{C}(\text{O})$).

General procedure D for the transprotection reactions. To a solution of the Alloc compound and Boc_2O (2 equiv) in CH_2Cl_2 was added $\text{Pd}(\text{PPh}_3)_4$ (0.02 equiv), immediately followed by the full amount of $n\text{-Bu}_3\text{SnH}$ (1.1 equiv) and the mixture was stirred at rt for 2 h. Concentration *in vacuo* and purification by *fc* (first with hexane, then with the suitable eluent) afforded the pure product(s).

rel-(3*S*,5*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (65). Following the general procedure D, a solution of **35** (760 mg, 2.16 mmol) in CH₂Cl₂ (25 mL) was treated with Boc₂O (990 μ L, 4.31 mmol), Pd(PPh₃)₄ (50 mg, 0.043 mmol) and *n*-Bu₃SnH (629 μ L, 2.37 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded **65** (612 mg, 1.66 mmol, 77%) as a light yellow oil, *R*_f 0.35. IR ν 1740, 1680, 1360, 690; ¹H NMR (200 MHz) δ 1.43 (s, 9 H, (CH₃)₃), 2.47–2.69 (m, 2 H, 2 \times H₄), 3.11 (dd, *J* = 8.1, 10.6 Hz, 1 H, CHHCl), 3.30–3.44 (m, 2 H, CHHCl and H₅), 3.77 (d, *J* = 12.6 Hz, 1 H, CHHPh), 3.81 (s, 3 H, CO₂CH₃), 4.23 (d, *J* = 12.6 Hz, 1 H, CHHPh), 4.59 (t, *J* = 8.8 Hz, 1 H, H₃), 7.27–7.47 (m, 5 H, ArH).

rel-(3*R*,5*S*)-2-(*tert*-Butoxycarbonyl)-5-chloromethyl-3-pyrazolidinecarboxylic acid methyl ester (66). A mixture of **65** (120 mg, 0.33 mmol), Pd/C (30 mg of 10% Pd on C, 0.03 mmol) and a few drops of a 1 M HCl/MeOH solution in MeOH (10 mL) was stirred under a H₂-atmosphere for 1 h. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in aq satd NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 \times 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:1) to afford **66** (81 mg, 0.29 mmol, 90%) white solid, mp 45–47 °C, *R*_f 0.15. IR ν 1740, 1705, 1365, 1130; ¹H NMR (200 MHz) δ 1.45 (s, 9 H, (CH₃)₃C), 2.23 (ddd, *J* = 13.2, 7.1, 5.1 Hz, 1 H, H₄), 2.54 (ddd, *J* = 13.2, 9.2, 4.4 Hz, 1 H, H₄), 3.43 (dd, *J* = 11.2, 7.3 Hz, 1 H, CHHCl), 3.60 (dd, *J* = 11.2, 4.8 Hz, 1 H, CHHCl), 3.75 (s, 3 H, CO₂CH₃), 3.66–3.77 (m, 1 H, H₅), 4.59 (dd, *J* = 4.9, 9.1 Hz, 1 H, H₃); ¹³C NMR (50 MHz) δ 28.3 ((CH₃)₃C), 35.7 (C₄), 44.9 (CH₂Cl), 52.4 (CO₂CH₃), 59.0, 59.2 (C₃ and C₅), 81.1 ((CH₃)₃C); MS (EI, 70 eV) *m/z* (relative intensity) 178 (M⁺, 100, 90), 119 (100), 95 (45), 91 (100), 69 (60).

Crystallographic data.

Tetragonal, *P* 4₂₁*c*, *a* = *b* = 17.4709(7), *c* = 9.695 Å, α = β = γ = 90°, *V* = 2959.3(2) Å³, *Z* = 8, *D*_x = 1.25 g cm^{−3}, λ (CuK α) = 1.5418 Å, μ (CuK α) = 23.98 cm^{−1}, *F*(000) = 1184, rt. Final *R* = 0.076 for 1164 observed reflections.

Table 7.3. Bond distances of the atoms (Å), with standard deviations in parentheses.

C1–C4	1.777(8)	C7–N2	1.337(8)	C2–H21	1.07(6)	C9–H92	1.10(4)
C1–C2	1.553(9)	C7–O3	1.193(8)	C2–H22	1.11(3)	C9–H93	1.07(7)
C1–H4	1.51(1)	C7–O4	1.366(7)	C3–H3	1.06(4)	C10–H101	1.09(5)
C1–N1	1.467(8)	C8–C9	1.49(1)	C4–H41	1.07(4)	C10–H102	1.08(4)
C2–C3	1.548(9)	C8–C10	1.52(1)	C4–H42	1.08(6)	C10–H103	1.08(4)
C3–C5	1.496(9)	C8–C11	1.51(1)	C6–H61	1.08(7)	C11–H111	1.10(3)
C3–N2	1.441(8)	C4–O8	1.489(8)	C6–H62	1.10(4)	C11–H112	1.09(4)
C5–O1	1.21(1)	N1–N2	1.420(6)	C6–H63	1.09(6)	C11–H113	1.07(5)
C5–O2	1.306(9)	C1–H1	1.05(4)	C9–H91	1.08(5)	N1–H2	1.06(5)
C6–O2	1.47(1)						

Table 7.4. Bond angles of the atoms (°), with standard deviations in parentheses.

C2–C1–C4	113.6(5)	C1–N1–N2	103.4(4)	H61–C6–H63	90(5)
C2–C1–N1	104.4(5)	C5–O2–C6	114.5(6)	H62–C6–H63	145(5)
C4–C1–N1	107.2(5)	C7–O4–C8	121.1(5)	C8–C9–H91	100(3)
C1–C2–C3	103.0(5)	C2–C1–H1	106(2)	C8–C9–H92	99(4)

C2-C3-C5	108.9(5)	C4-C1-H1	111(3)	C8-C9-H93	98(4)
C2-C3-N2	103.1(5)	N1-C1-H1	115(2)	H91-C9-H92	128(5)
C5-C3-N2	115.8(6)	C1-C2-H21	97(4)	H91-C9-H93	115(6)
Cl-C4-C1	112.2(5)	C1-C2-H22	107(3)	H92-C9-H93	110(5)
C3-C5-O1	121.5(7)	C3-C2-H21	107(4)	C8-C10-H101	99(3)
C3-C5-O2	114.4(6)	C3-C2-H22	113(3)	C8-C10-H102	103(3)
O1-C5-O2	124.1(7)	H21-C2-H22	126(5)	C8-C10-H103	105(3)
N2-C7-O3	126.4(6)	C2-C3-H3	122(3)	H101-C10-H102	115(4)
N2-C7-O4	107.7(5)	C5-C3-H3	106(2)	H101-C10-H103	123(4)
O3-C7-O4	125.8(6)	N2-C3-H3	101(3)	H102-C10-H103	109(4)
C9-C8-C10	110.0(6)	Cl-C4-H41	94(3)	C8-C11-H111	102(4)
C9-C8-C11	112.0(6)	Cl-C4-H42	118(4)	C8-C11-H112	105(2)
C9-C8-O4	109.0(5)	C1-C4-H41	116(3)	C8-C11-H113	115(3)
C10-C8-C11	113.0(6)	C1-C4-H42	101(4)	H111-C11-H112	110(5)
C10-C8-O4	102.3(5)	H41-C4-H42	118(5)	H111-C11-H113	129(6)
C11-C8-O4	110.1(5)	O2-C6-H61	95(4)	H112-C11-H113	94(4)
C3-N2-C7	126.5(5)	O2-C6-H62	97(3)	C1-N1-H2	107(4)
C3-N2-N1	114.3(4)	O2-C6-H63	100(4)	N2-N1-H2	108(4)
C7-N2-N1	118.9(5)	H61-C6-H62	118(5)		

rel-(3*R*,5*S*)-5-chloromethyl-3-pyrazolidinecarboxylic acid hydrogen chloride (67). A solution of 66 (30 mg, 0.11 mmol) in 2 M HCl was heated at 60 °C for 2 h and concentrated *in vacuo* to afford 67 (18 mg, 0.090 mmol, 82%) as a viscous yellow oil. ^1H NMR (200 MHz, D_2O) δ 2.46 (dt, $J = 13.8, 8.4$ Hz, 1 H, H4), 2.67 (ddd, $J = 4.5, 7.8, 13.9$ Hz, 1 H, H4), 3.74 (dd, $J = 7.5, 12.4$ Hz, 1 H, CHHCl), 3.90 (dd, $J = 3.8, 12.3$ Hz, 1 H, CHHCl), 4.08–4.20 (m, 1 H, H5), 4.49 (dd, $J = 4.4, 8.9$ Hz, 1 H, H3); ^{13}C NMR (50 MHz, D_2O) δ 34.9 (C4), 44.8 (CH_2Cl), 62.4, 62.6 (C3 and C5), 174.5 (C(O)).

rel-(3*S*,4*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-4-(1-chloroethyl)-3-pyrazolidinecarboxylic acid methyl ester (68). According to the general procedure D, a solution of 41 (90 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (124 μL , 0.54 mmol), $\text{Pd}(\text{PPh}_3)_4$ (8.5 mg, $7.4 \cdot 10^{-3}$ mmol) and *n*- Bu_3SnH (72 μL , 0.27 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded 68 (49 mg, 0.13 mmol, 54%) as a light yellow oil, R_f 0.35. IR ν 1745, 1700, 1680, 690; ^1H NMR (200 MHz) δ 1.39 (s, 9 H, $(\text{CH}_3)_3\text{C}$), 1.56 (d, $J = 6.7$ Hz, 3 H, CH_3), 3.03–3.10 (m, 3 H, H4 and 2 \times H5), 3.69–3.85 (m, 2 H, CH_2Ph), 3.82 (s, 3 H, CO_2CH_3), 4.15–4.30 (m, 2 H, H3 and CHCl), 7.26–7.46 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ 24.1 (CH_3), 28.2 ($(\text{CH}_3)_3\text{C}$), 51.5 (C4), 52.6 (CO_2CH_3), 54.5 (C5), 57.5 (CHCl), 61.8 (CH_2Ph), 63.2 (C3), 81.0 ($(\text{CH}_3)_3\text{C}$), 127.4, 128.3, 129.6 (ArH), 137.5 (ArC), 172.9 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 382 (M^+ , 4), 281 (58), 245 (15), 231 (9), 91 (100); HRMS calcd for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_4\text{Cl}$ 382.1659, found 382.1635.

1-Benzyl-2-(*tert*-butoxycarbonyl)-5-chlorohexahydro-1*H*-diazepine-3-carboxylic acid methyl ester (69). According to the general procedure D, a solution of 42 (76 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (105 μL , 0.46 mmol), $\text{Pd}(\text{PPh}_3)_4$ (7.2 mg, $6.2 \cdot 10^{-3}$ mmol) and *n*- Bu_3SnH (60 μL , 0.23 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 69 (51 mg, 0.13 mmol, 64%) as a colorless oil, R_f 0.50. IR ν 1740, 1680, 690; ^1H NMR (200 MHz) δ 1.38 (s, 9 H, $(\text{CH}_3)_3\text{C}$), 1.45–1.65 (m, 2 H, 2 \times H6), 2.19 (dd, $J = 12.8, 8.9$ Hz, 1 H, H4), 2.59 (ddd, $J = 13.0, 9.3, 7.0$ Hz, 1 H, H4), 3.20–3.55 (m, 3 H, H5 and 2 \times H7), 3.68 (d, $J = 12.3$ Hz, 1 H, CHHPh), 3.80 (s, 3 H, CO_2CH_3), 4.13 (d, $J = 13.0$ Hz, 1 H, CHHPh), 4.50 (t, $J = 8.8$ Hz, 1 H, H3), 7.22–7.44 (m, 5 H, ArH); ^{13}C NMR (50 MHz) δ (two diastereomers) 28.2 ($(\text{CH}_3)_3\text{C}$), 30.5, 34.4, 36.0, 35.9 (C4 and C6), 41.9 (C7), 52.4 (CO_2CH_3), 59.5 (C3),

60.2 (C5), 61.4 (CH₂Ph), 80.6 ((CH₃)₃C), 127.3, 128.1, 129.8 (ArH), 137.6 (ArC), 173.4 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 382 (M⁺, 3), 327 (20), 281 (58), 163 (10), 91 (100).

Deprotection of 44. Following the general procedure D, a solution of 44 (200 mg, 0.55 mmol) in CH₂Cl₂ (3 mL) was treated with Boc₂O (139 μ L, 0.61 mmol), Pd(PPh₃)₄ (13 mg, 0.011 mmol) and *n*-Bu₃SnH (160 μ L, 0.61 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded 3-benzyl-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-1-phthalazinecarboxylic acid methyl ester (70) (118 mg, 0.31 mmol, 56%) as a colorless oil, *R_f* 0.35 and 3-benzyl-3,4-dihydro-1-phthalazinecarboxylic acid methyl ester (71) (35 mg, 0.12 mmol, 22%) as a colorless oil, *R_f* 0.32. 70: IR ν 1735, 1670, 1130, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 1.52, 1.53 (s, 9 H, (CH₃)₃C), 3.30–4.50 (br m, 7 H, CO₂CH₃, CH₂Ph and NCH₂), 5.40, 5.60 (br s, 1 H, NCH), 7.00–7.50 (m, 9 H, ArH); ¹³C NMR (63 MHz) δ 28.4 ((CH₃)₃C), 52.4 (CO₂CH₃), 52.8 (NCH), 55.6 (NCH₂), 59.1 (CH₂Ph), 81.3 ((CH₃)₃C), 126.1, 127.4, 127.9, 128.3, 129.4, 131.7 (ArH), 132.0, 136.1, 138.0 (ArC), 171.5 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 382 (M⁺, 20), 282 (61), 223 (45), 91 (100), 57 (83); HRMS calcd for C₂₂H₂₆N₂O₄ 382.1892, found 382.1901. 71: IR ν 1700, 1435, 1135, 690; ¹H NMR (200 MHz) δ 3.94 (s, 3 H, CO₂CH₃), 4.08 (s, 2 H, NCH₂), 4.69 (s, 2 H, CH₂Ph), 6.89–6.94 (m, 1 H, ArH), 7.23–7.40 (m, 7 H, ArH), 8.08–8.13 (m, 1 H, ArH).

1-Benzyl-3-methylene-1,4,5,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (72). According to the general procedure D, a solution of 45 (100 mg, 0.30 mmol) in CH₂Cl₂ (3 mL) was treated with Boc₂O (153 μ L, 0.67 mmol), Pd(PPh₃)₄ (11 mg, 9.1·10⁻³ mmol) and *n*-Bu₃SnH (88 μ L, 0.33 mmol). Concentration *in vacuo* and flash chromatography (ethyl acetate/hexane 1:4) afforded 72 (58 mg, 0.24 mmol, 78%) as a colorless oil, *R_f* 0.25. ¹H NMR (200 MHz) δ 3.14 (s, 2 H, 2 × H4), 3.43 (s, 2 H, 2 × H6), 3.84 (s, 3 H, CO₂CH₃), 4.61 (s, 2 H, CH₂Ph), 4.93 (s, 1 H, C=CHH), 5.03 (s, 1 H, C=CHH), 7.24–7.35 (m, 5 H, ArH).

***rel*-(3*R*,4*S*,5*S*)-1-Benzyl-2-(*tert*-butoxycarbonyl)-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (73).** Following the general procedure D, a solution of 48 (434 mg, 1.02 mmol) in CH₂Cl₂ (15 mL) was treated with Boc₂O (0.52 mL, 2.25 mmol), Pd(PPh₃)₄ (35 mg, 0.031 mmol) and *n*-Bu₃SnH (0.30 mL, 1.13 mmol). Concentration *in vacuo* and fc (ethyl acetate/hexane 1:4) afforded 73 (288 mg, 0.65 mmol, 64%) as a light yellow oil, *R_f* 0.60. IR ν 1760, 1690, 1250, 840, 690; ¹H NMR (200 MHz) δ 0.11 (s, 9 H, (CH₃)₃Si), 1.45 (s, 9 H, (CH₃)₃C), 1.97 (t, *J* = 9.0 Hz, 1 H, H4), 3.06 (dd, *J* = 11.4, 4.3 Hz, 1 H, CHHCl), 3.24 (dd, *J* = 11.4, 3.4 Hz, 1 H, CHHCl), 3.43–3.50 (m, 1 H, H5), 3.77 (s, 3 H, CO₂CH₃), 3.96 (d, *J* = 12.7 Hz, 1 H, CHHPh), 4.32 (d, *J* = 12.7 Hz, 1 H, CHHPh), 4.99 (d, *J* = 9.0 Hz, 1 H, H3), 7.26–7.51 (m, 5 H, ArH); ¹³C NMR (50 MHz) δ 1.7 ((CH₃)₃Si), 28.3 ((CH₃)₃C), 35.1 (C4), 47.9 (CH₂Cl), 52.0 (CO₂CH₃), 62.0 (C3), 63.2 (CH₂Ph), 68.7 (C5), 80.8 ((CH₃)₃C), 127.4, 128.2, 129.4 (ArH), 138.1 (ArC), 155.7, 172.8 (C(O)); MS (EI, 70 eV) *m/z* (relative intensity) 440 (M⁺, 26), 340 (90), 325 (12), 185 (13), 159 (5), 133 (8), 91 (100); HRMS calcd for C₂₁H₃₃N₂O₄ClSi 440.1898, found 440.1905.

2-(*tert*-Butoxycarbonyl)-5-chlorohexahydro-1*H*-diazepine-3-carboxylic acid methyl ester (74). A mixture of 69 (40 mg, 0.10 mmol), Pd/C (11 mg of 10% Pd on C, 0.01 mmol) and one drop of a 3 M HCl/MeOH solution in MeOH (5 mL) was stirred under a H₂-atmosphere for 1 h. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in aq satd NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:2) to afford 74 (20 mg, 0.065 mmol, 65%) as a colorless oil, *R_f* 0.25. IR ν 3450, 1720, 1685; ¹H NMR (200 MHz) δ 1.45 (s, 9 H, (CH₃)₃), 1.69–1.84 (m, 2 H, 2 × H6), 2.19–2.27 (m, 2 H, 2 × H4), 3.53–3.78 (m, 3 H, H5 and 2 × H7), 3.75 (s, 3 H, CO₂CH₃), 4.50–4.63 (m, 1 H, H3); ¹³C NMR (50 MHz) δ (mixture of isomers) 28.0 ((CH₃)₃C), 30.5, 35.6, 35.8, 38.2, 38.3 (C4 and C6), 42.0 (C7), 52.1 (CO₂CH₃), 56.0, 56.5 (C5), 58.8 (C3), 80.9 ((CH₃)₃C), 172.7 (C(O)); MS (EI, 70 eV) *m/z*

(relative intensity) 292 (M^+ , 6), 236 (8), 192 (20), 175 (13), 167 (23), 153 (27), 131 (100).

rel-(3*R*,4*S*,5*S*)-2-(*tert*-Butoxycarbonyl)-5-chloromethyl-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (75). A mixture of **73** (275 mg, 0.63 mmol), Pd/C (67 mg of 10% Pd on C, 0.06 mmol) and a few drops of a 3 M HCl/MeOH solution in MeOH (7 mL) was stirred under a H_2 -atmosphere for 45 min. After filtration over Celite, the solution was concentrated *in vacuo*, taken up in aq satd $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed (ethyl acetate/hexane 1:2) to afford **75** (178 mg, 0.51 mmol, 81%) as a colorless oil, R_f 0.50. IR ν 1735, 1700, 1250, 840; 1H NMR (200 MHz) δ 0.10 (s, 9 H, $(CH_3)_3Si$), 1.45 (s, 9 H, $(CH_3)_3C$), 1.84 (t, $J = 9.0$ Hz, 1 H, H4), 3.57–3.84 (m, 6 H, CO_2CH_3 , H5 and CH_2Cl), 4.65 (d, $J = 8.8$ Hz, 1 H, H3); ^{13}C NMR (50 MHz) δ 1.7 ($(CH_3)_3Si$), 28.2 ($(CH_3)_3C$), 36.1 (C4), 45.2 (CH_2Cl), 51.8 (CO_2CH_3), 60.6 (C3), 63.0 (C5), 81.1 ($(CH_3)_3C$), 153.2, 172.0 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 350 (M^+ , 8), 279 (9), 250 (100), 191 (47), 185 (19), 133 (18); HRMS calcd for $C_{14}H_{27}N_2O_4ClSi$ 350.1429, found 350.1468.

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